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 Plus - Filmtabletten	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 1220 Wien Austria	Fortzaar	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels Belgium	COZAAR PLUS FORTE 100 MG/25 MG	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels Belgium	COZAAR PLUS 50 MG/12,5 MG	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Belgium	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN PLUS FORTE 100 MG/25 MG	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Belgium	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN PLUS 50 MG/12,5 MG	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	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	Hyzaar	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Cyprus	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	FORTZAAR	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Cyprus	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	HYZAAR	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	Cozaar Comp.	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	Cozaar Comp. Forte	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	Cozaar Comp. 100 mg / 12,5 mg	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	Fortzaar	100 mg losartan potassium – 25 mg hydrochlorothiazide	Film-coated tablets	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46, Tallinn 11415, Estonia	HYZAAR	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46, Tallinn 11415, Estonia	FORTZAAR	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2031 BN Haarlem The Netherlands	Cozaar Comp	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	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 2031 BN Haarlem The Netherlands	Cozaar Comp	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2031 BN Haarlem The Netherlands	Cozaar Comp Forte	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08 France	Fortzaar 100 mg/25 mg film-coated tablets	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08 France	Hyzaar 100 mg/25 mg film-coated tablets	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08 France	Fortzaar 50 mg/12,5 mg film-coated tablets	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08 France	Hyzaar 50 mg/12,5 mg film-coated tablets	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08 France	Fortzaar 100 mg/12,5 mg film-coated tablets	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	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 PLUS 50/12,5 mg Filmtabletten	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	CARDOPAL PLUS 50/12,5 mg Filmtabletten	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Germany	VARIPHARM ARZNEIMITTEL GMBH Lindenplatz 1 85540, Haar Germany	LORZAAR VARIPHARM PLUS 50/12,5 mg Filmtabletten	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	FORTZAAR 100/25 mg Filmtabletten	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Germany	VARIPHARM ARZNEIMITTEL GMBH Lindenplatz 1 85540, Haar, Germany	FORTZAAR VARIPHARM 100/25 mg Filmtabletten	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	LORZAAR PLUS forte 100/12,5 mg Filmtabletten	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671, Greece	HYZAAR	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671, Greece	HYZAAR 100/25	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Hungary	Merck Sharp & Dohme Hungary Ltd 50, Alkotas str. H-1123 Budapest Hungary	Hyzaar 50/12.5 mg	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	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	Hyzaar Forte 100/25 mg	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	COZAAR-COMP 50/12.5MG	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	COZAAR-COMP Forte	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	COZAAR-COMP 100/12.5MG	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Ireland	Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU United Kingdom	'Cozaar' Comp 50mg/12.5mg film-coated tablets	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Ireland	Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU United Kingdom	Cozaar' Comp 100mg/25mg film-coated tablets	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Italy	Merck Sharp & Dohme Italia S.p.A. via G Fabbroni 6 , 00191 Rome Italy	HIZAAR 50 mg + 12,5 mg compresse rivestite con film	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Italy	Merck Sharp & Dohme Italia S.p.A. via G Fabbroni 6 , 00191 Rome Italy	HIZAAR 100 mg + 25 mg compresse rivestite con film	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Merck Sharp & Dohme (Italia) S.p.A. Via G Fabbroni 6, 00191 Rome Italy	FORZAAR 100 mg + 25 mg compresse rivestite con film	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 00191 Rome, Italy	NEO-LOTAN PLUS 50 mg + 12,5 mg compresse rivestite con film	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Italy	Neopharmed S.p.A. Via G. Fabbroni, 6 00191 Rome, Italy	NEO-LOTAN PLUS 100 mg + 25 mg compresse rivestite con film	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- viale Shakespeare 47, 00144 Rome, Italy	LOSAZID 50 mg + 12,5 mg compresse rivestite con film	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	oral use
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- viale Shakespeare 47, 00144 Rome, Italy	LOSAZID 100 mg + 25 mg compresse rivestite con film	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	oral use
Latvia	SIA Merck Sharp & Dohme Latvia, Latvija; Skanstes street 13, LV-1013, Riga, Latvia	HYZAAR 50 mg/12,5 mg	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	oral use
Latvia	SIA Merck Sharp & Dohme Latvia, Latvija; Skanstes street 13, LV-1013, Riga, Latvia	Fortzaar 100 mg/25 mg	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	oral use
Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius Lithuania	FORTZAAR (Losartan/Hydrochlorothiazide)	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius Lithuania	HYZAAR (Losartan/Hydrochlorothiazide)	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR PLUS FORTE 100 MG/25 MG	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR PLUS 50 MG/12,5 MG	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN PLUS FORTE 100 mg/25 mg	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN PLUS 50 mg/12,5 mg	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Malta	Merck Sharp & Dohme Ltd., Hertfordshire Road, Hoddesdon, Hertfordshire, EN11 9BU United Kingdom	"Cozaar Comp" 50/12.5 mg pilloli miksija b'rita	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Malta	Merck Sharp & Dohme Ltd., Hertfordshire Road, Hoddesdon, Hertfordshire, EN11 9BU, United Kingdom	"Cozaar Comp" 100/12,5 mg pilloli miksija b'rita	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Malta	Merck Sharp & Dohme Ltd., Hertfordshire Road, Hoddesdon, Hertfordshire, EN11 9BU United Kingdom	"Cozaar Comp" 100/25 mg pilloli miksija b'rita	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar Plus 100/12,5	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
The Netherlands	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Fortzaar 100/25	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Hyzaar 50/12,5	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Norway	MSD BV Waarderweg 39 2031 BN Haarlem The Netherlands	Cozaar Comp	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Norway	MSD BV Waarderweg 39 2031 BN Haarlem The Netherlands	Cozaar Comp	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Norway	MSD BV Waarderweg 39 2031 BN Haarlem The Netherlands	Cozaar Comp Forte	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warsaw Poland	HYZAAR	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. ul. Chłodna 51 00-867 Warsaw Poland	HYZAAR FORTE	100 mg losartan potassium - 25 mg hydrochlorothiazide	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 Plus	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	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 Plus	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	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	FORTZAAR	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Portugal	Heptafarma- Companhia Farmacêutica, Sociedade Unipessoal, Lda Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos, Portugal	SIAARA	100 mg losartan potassium - 25 mg hydrochlorothiazide	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 Plus	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	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 Plus	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Portugal	Frosst Portuguesa – Produtos Farmacêuticos, Lda. Quinte da Fonte Edificio Vasco da Gama, 19 P.O. BOX 214 Porto Salvo 2780-730 Paço d´Arcos Portugal	Losartan + Hidroclorotiazida Frosst	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	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	HYZAAR® 50 mg/12,5 mg, comprimate filmate	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	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	FORTZAAR® 100/25 mg, comprimate filmate	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Smartinska cesta 140, 1000 Ljubljana Slovenia	HYZAAR	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Smartinska cesta 140, 1000 Ljubljana Slovenia	HYZAAR	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Smartinska cesta 140, 1000 Ljubljana Slovenia	FORTZAAR	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 MADRID Spain	Cozaar Plus	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 MADRID Spain	Fortzaar	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar Comp 50 mg/12,5 mg filmdragerade tabletter	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar Comp 100 mg/12,5 mg filmdragerade tabletter	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar Comp Forte 100 mg/25 mg filmdragerade tabletter	100 mg losartan potassium - 25 mg hydrochlorothiazide	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-COMP 50/12.5MG FILM COATED TABLETS	50 mg losartan potassium - 12.5 mg hydrochlorothiazide	Film-coated tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU, United Kingdom	COZAAR-COMP 100/25MG FILM COATED TABLETS	100 mg losartan potassium - 25 mg hydrochlorothiazide	Film-coated tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU, United Kingdom	COZAAR-Comp 100 mg/12.5 mg Film-coated tablets	100 mg losartan potassium - 12.5 mg hydrochlorothiazide	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 COMP. AND ASSOCIATED NAMES (SEE ANNEX I)

Cozaar Comp. and Cozaar Comp Forte (losartan/hydrochlorothiazide) have been included in the list of products for Summary of Products Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended. Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned products (and its associated names), Denmark notified the CHMP/EMEA Secretariat of an official referral under Article 30 of Directive 2001/83/EC as amended in order to resolve divergences amongst the nationally authorised SPCs and thus to harmonise its divergent SPCs across the EU.

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. Hydrochlorothiazide (HCTZ) is a thiazide diuretic which has also been used as an antihypertensive agent. The diuretic action of HCTZ reduces plasma volume, with consequent increase in plasma renin activity, increase in adolsterone secretion, increase in urinary K+ and HCO-3 loss, and decrease in plasma K+.

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 in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy
The efficacy and safety are established for the indication “treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy”. Therefore the CHMP considered that this indication is acceptable.

- As First step treatment in patients with moderate to severe hypertension and in patients with high or very high Left Ventricular Hypertrophy
The CHMP concluded that the indication for the initial therapy of hypertension with the fixed dose combination (FDC) does not have a positive benefit-risk ratio, and therefore is not acceptable.

The data available do not show that a first line therapy with the FDC is of advantage as compared to a stepwise approach within the approved indication. There was no relevant difference in the number of patients with severe hypertension showing a relevant BP lowering effect during the first 4 weeks. More than 50% of those patients reaching the target BP on the FDC within 4 weeks did not require a combination. These patients (9.4%) would have been over-treated on a FDC on a long term basis. When compared to only 8.2% of patients that can reach target BP somewhat faster compared to a stepwise approach, the risk benefit ratio is negative both for patients with severe and for patients with mild to moderate hypertension.

As the MAH did not submit data to demonstrate a clear population that would benefit from the FDC with regards to cardiovascular outcome, the benefit/risk of the indication in first line could be assessed and the indication is not warranted by the CHMP.

- Reduction in risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy.
During the referral procedure, the MAH proposed amending the indication to substitute “cardiovascular morbidity and mortality” with “stroke”. 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, whilst the proposed indication for losartan monotherapy 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", the following considerations apply for the FDC:

The CHMP was concerned that there is no evidence that supports each of the two substances in Cozaar Comp (losartan and HCTZ) having a documented contribution to the claimed indication as required by the The *NfG on fixed dose combination products*. In the losartan group 44% of the patients received HCTZ, in the atenolol group 38%. The MAH did not provide data showing that those patients receiving HCTZ had a clinical advantage with respect to clinical endpoints in comparison to those not receiving HCTZ. The MAH was asked to provide data on safety and efficacy for these subgroups of patients (Losartan, Atenolol, Losartan + HCTZ, Atenolol + HCTZ) in order to gain more insight into the contribution of HCTZ to the overall benefit risk ratio. In addition, a prevention indication for HCTZ alone, based on the LIFE data is not considered approvable.

Therefore, the CHMP considered that the benefit risk for the indication *Reduction in risk of cardiovascular morbidity and mortality (or risk of stroke) in hypertensive patients with left ventricular hypertrophy* is negative and this indication is not acceptable for the FDC.

Section 4.3 Contra-indications
The CHMP considered that the following contra-indications should be included in the SPC in all MSs: Severe renal impairment; Electrolyte disturbances such as hyponatremia, hypokalemia, hypercalcemia; Hyperuricaemia; Pregnancy and lactation; LAPP lactose deficiency; Liver insufficiency; Addison's disease. Given that the paediatric worksharing group is still ongoing, a definite working can only be implemented with respect to studies in children and adolescents after the procedure is finalised.

Section 4.4 Special warnings and precautions for use:
The CHMP considered that the following warnings should be included in the SPC in all MSs: Haemodialysis; Black patients; Obstructive valvular disease; Surgery/anaesthesia. Given that the paediatric worksharing group is still ongoing, a definite working can only be implemented with respecto to studies in children and adolescents after the procedure is finalised.

Pregnancy and Lactation
The CHMP considered that the text concerning pregnancy and lactation in the SPC (sections 4.3, 4.4 and 4.6) should 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.

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 indication:

- Treatment of hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide.

- the CHMP concluded that the data are not supportive of the following indications and therefore they should be removed from the marketing authorisation:

- as first step treatment in patients with moderate to severe hypertension and in patients with high or very high cardiovascular risk

- Reduction of cardiovascular morbidity and mortality (or risk of stroke) in hypertensive patients with left ventricular hypertrophy.

- 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 CHMP has recommended the amendment of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Cozaar Comp. 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 Comp and associated names (see Annex I) 50 mg/12.5 mg film-coated tablets
Cozaar Comp and associated names (see Annex I) 100 mg/12.5 mg film-coated tablets
Cozaar Comp and associated names (see Annex I) 100 mg/25 mg film-coated tablets

[To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cozaar Comp 50 mg/12.5 mg
Each tablet contains 50 mg of losartan (as potassium salt) and 12.5 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Cozaar Comp 100 mg/12.5 mg
Each tablet contains 100 mg of losartan (as potassium salt) and 12.5 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Cozaar Comp 100 mg/25 mg
Each tablet contains 100 mg of losartan (as potassium salt) and 25 mg of hydrochlorothiazide (HCTZ) as the active ingredients.

Excipients
Cozaar Comp 50 mg/12.5 mg
Each tablet contains 63.13 mg lactose monohydrate.
Cozaar Comp 100 mg/12.5 mg
Each tablet contains 88.40 mg lactose monohydrate.
Cozaar Comp 100 mg/25 mg
Each tablet contains 126.26 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

[To be implemented nationally]

3. PHARMACEUTICAL FORM

Film coated tablets

Cozaar Comp 50 mg/12.5 mg
Yellow, oval film-coated tablets marked 717 on one side and plain or scored on the other.
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Cozaar Comp 100 mg/12.5 mg
White, oval film-coated tablets marked 745 on one side and plain on the other.

Cozaar Comp 100 mg/25 mg
Light yellow, oval film-coated tablets marked 747 on one side and plain on the other.

[To be implemented nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cozaar Comp is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on losartan or hydrochlorothiazide alone.

4.2 Posology and method of administration

Cozaar Comp may be administered with other antihypertensive agents.
Cozaar Comp tablets should be swallowed with a glass of water
Cozaar Comp may be administered with or without food.

Hypertension
Losartan and hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose of Cozaar Comp is one tablet of Cozaar Comp 50 mg/12.5 mg (losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Cozaar Comp 50 mg/12.5 mg, the dosage may be increased to one tablet of Cozaar Comp 100 mg/25 mg (losartan 100 mg/ HCTZ 25 mg) once daily. The maximum dose is one tablet of Cozaar Comp 100 mg/25 mg once daily. In general, the antihypertensive effect is attained within three to four weeks after initiation of therapy. Cozaar Comp 100/12.5 (losartan 100 mg/ HCTZ 12.5 mg) is available for those patients titrated to 100 mg of Cozaar Comp who require additional blood pressure control.

Use in patients with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan and hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/HCTZ tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min) (see section 4.3).

Use in patients with intravascular volume depletion
Volume and /or sodium depletion should be corrected prior to administration of Losartan/HCTZ tablets.

Use in patients with hepatic impairment
Losartan/HCTZ is contraindicated in patients with severe hepatic impairment (see section 4.3.).

Use in the elderly
Dosage adjustment is not usually necessary for the elderly.

Use in children and adolescents (< 18 years)
There is no experience in children and adolescents. Therefore, losartan/hydrochlorothiazide should not be administered to children and adolescents.

4.3 Contraindications

- Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; Cholestasis and biliary obstructive disorders

- Refractory hyponatraemia
- Symtomatic hyperuricaemia/gout
- 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
- Lactation (see section 4.6)
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)
- Anuria

4.4 Special warnings and precautions for use

Losartan

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 Intravascular volume depletion
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Cozaar Comp tablets (see sections 4.2. and 4.3.).

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and 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/ hydrochlorothiazide 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, Cozaar Comp should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore Cozaar Comp is contraindicated in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone 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.

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 Cozaar Comp 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.

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

Ethnic differences
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.

Pregnancy
Cozaar Comp should not be initiated during pregnancy. Unless continued Losartan/HTCZ 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 Cozaar Comp should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Cozaar Comp is contraindicated for patients with severe hepatic impairment (see section 4.3 and 5.2).

Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Excipient
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 6.1**).**

4.5 Interaction with other medicinal products and other forms of interaction

Losartan

Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

As with other medicines which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

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.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

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.

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive drugs
Additive effect.

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (eg cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates
In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa
There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Losartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes

(ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Laboratory Test Interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine
Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine Contrast Media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product.
Patients should be rehydrated before the administration.

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Pregnancy and lactation

Pregnancy
The use of Cozaar Comp is not recommended during the first trimester of pregnancy (see section 4.4).
The use of Cozaar Comp 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 Cozaar Comp should be stopped immediately and, if appropriate, alternative therapy should be started.
Cozaar Comp 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 Cozaar Comp have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken Cozaar Comp should be closely observed for hypotension (see also section 4.3 and 4.4).
Hydrochlorothiazide may reduce both plasma volume and uteroplacental blood flow. Thiazides pass the placental barrier and are found in cord blood. They may cause fetal electrolyte disturbances and

possibly other reactions that have been observed in adults. Cases of thrombocytopenia in neonates and fetal or neonatal jaundice were reported after treating the mothers with thiazides.

Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Thiazides pass into human milk and may inhibit lactation. Because of the potential for adverse effects on the nursing infant, Cozaar Comp 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 adverse events below are classified where appropriate by system organ class and frequency according to 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: ≤ 1/10,000
(cannot be estimated from the available data)

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse events peculiar to this combination of substances were observed. The adverse events were restricted to those which were formerly observed with losartan potassium salt and/or hydrochlorothiazide.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as substance-related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan and hydrochlorothiazide.

Next to these effects, there are further adverse reactions reported after the introduction of the product to the market as follows:

Hepato-biliary disorders
Rare: Hepatitis

Investigations
Rare: Hyperkalaemia, elevation of ALT

Additional adverse events that have been seen with one of the individual components and may be potential adverse events with losartan potassium/ hydrochlorothiazide are the following:

Losartan

Blood and lymphatic system disorders
Uncommon: Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

Immune system disorders
Rare: Anaphylactic reactions, angioedema, urticaria

Metabolism and nutrition disorders
Uncommon: Anorexia, gout

Psychiatric disorders
Common: Insomnia
Uncommon: Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment

Nervous system disorders
Common: Headache, dizziness
Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

Eye disorders
Uncommon: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus

Cardiac disorders
Uncommon: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Vascular disorders
Uncommon: Vasculitis

Respiratory, thoracic and mediastinal disorders
Common: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder
Uncommon: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Gastrointestinal disorders
Common: Abdominal pain, nausea, diarrhoea, dyspepsia
Uncommon: Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting

Hepato-biliary disorders
Not known: Liver function abnormalities

Skin and subcutaneous tissue disorders
Uncommon: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

Musculoskeletal and connective tissue disorders
Common: Muscle cramp, back pain, leg pain, myalgia
Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness

Renal and urinary disorders
Uncommon: Nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders
Uncommon: Decreased libido, impotence

General disorders and administration site conditions
Common: Asthenia, fatigue, chest pain

Uncommon: Facial oedema, fever

Investigations
Common: Hyperkalaemia, mild reduction of haematocrit and haemoglobin
Uncommon: Mild increase in urea and creatinine serum levels
Very rare: Increase in hepatic enzymes and bilirubin.

Hydrochlorothiazide

Blood and lymphatic system disorders
Uncommon: Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia

Immune system disorders
Rare: Anaphylactic reaction

Metabolism and nutrition disorders
Uncommon: Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Psychiatric disorders
Uncommon: Insomnia

Nervous system disorders
Common: Cephalalgia

Eye disorders
Uncommon: Transient blurred vision, xanthopsia
Vascular disorders
Uncommon: Necrotizing angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
Uncommon: Respiratory distress including pneumonitis and pulmonary oedema

Gastrointestinal disorders
Uncommon: Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

Hepato-biliary disorders
Uncommon: Icterus (intrahepatic cholestatis), pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

Renal and urinary disorders
Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administration site conditions
Uncommon: Fever, dizziness

4.9 Overdose

No specific information is available on the treatment of overdosage with Cozaar Comp. Treatment is symptomatic and supportive. Therapy with Cozaar Comp should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and

correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination containing an angiotensin II-receptor(type AT1)-antagonist and a thiazide diuretic, Antihypertensive, ATC code: C09DA01

Losartan-Hydrochlorothiazide

The components of Cozaar Comp have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

The antihypertensive effect of Cozaar Comp is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Cozaar Comp had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

Cozaar Comp is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is effective in all degrees of hypertension.

Losartan

Losartan is a synthetically produced oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormon 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 thus no increase in bradykinin-mediated undesirable effects.

During the administration of losartan the 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 the plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan,PRA and angiotensin II values fell within 3 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.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In nondiabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent in chronic therapy.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive hemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. The occurrence of hypotension was dose related in these heart failure patients.

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.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.

5.2 Pharmacokinetic properties

Absorption

Losartan
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. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan
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, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan
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 of ^{14}C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan-Hydrochlorothiazide
The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan
Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Neither losartan nor the active metabolite can be removed by hemodialysis.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of

losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F_1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including renal toxicity and foetal death, occurred when pregnant rate were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cozaar Comp 50 mg/12.5 mg, Cozaar Comp 100 mg/12.5 mg and Cozaar Comp 100 mg/25 mg:
Each tablet contains the following inactive ingredients:
microcrystalline cellulose(E460),
lactose monohydrate,
pregelatinized maize starch,
magnesium stearate (E572),
hydroxypropyl cellulose (E463),
hypromellose(E464).

Cozaar Comp 50 mg/12.5 mg contains 4.24 mg (0.108 mEq) of potassium.
Cozaar Comp 100 mg/12.5 mg mg contains 8.48 mg (0.216 mEq) of potassium.
and Cozaar Comp 100 mg/25 mg contains 8.48 mg (0.216 mEq) of potassium.

Cozaar Comp 50 mg/12.5 mg and Cozaar Comp 100 mg/25 mg also contain, Titanium dioxide (E171), Quinoline yellow aluminum lake (E104), and Carnauba wax (E903)

Cozaar Comp 100 mg/12.5 mg also contain: white color concentrate (or the individual ingredients of the concentrate: hydroxypropyl cellulose, hypromellose and titanium dioxide) and carnauba wax. Carnauba wax (E903), Titanium dioxide (E171)

Cozaar Comp 100 mg/25 mg also contain:, Titanium dioxide (E171), Quinoline yellow aluminum lake (E104), and Carnauba wax (E903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Cozaar Comp 50 mg/12.5 mg, Cozaar Comp 100 mg/25 mg:

3 years

Cozaar Comp 100 mg/12.5 mg:

2 years

6.4 Special precautions for storage

Store in the original package. Keep the blister in the outer carton and the keep the bottle tightly closed.

6.5 Nature and contents of container

Cozaar Comp 50 mg/12.5 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, or 280 tablets. HDPE bottles of 100 tablets.

Cozaar Comp 100 mg/12.5 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 14, 15, 28, 30, 50, 56, 84, 90, 98, 280 tablets. HDPE bottles of 100 tablets.

Cozaar Comp 100 mg/25 mg> - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 14, 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 <and other handling>

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 Comp 50 mg/12.5 mg film-coated tablets blister

1. NAME OF THE MEDICINAL PRODUCT

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

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg losartan potassium and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, or 280 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 package. 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 Comp 50 mg/12.5 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 50 mg/12.5 mg

Losartan and hydrochlorothiazide

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 Comp 50 mg/12.5 mg film-coated tablets HDPE Bottle

1. NAME OF THE MEDICINAL PRODUCT

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

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg losartan potassium and 12.5 mg hydrochlorothiazide.

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. Keep the bottle tightly closed.

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 Comp 50 mg/12.5 mg film-coated tablets HDPE Bottle

1. NAME OF THE MEDICINAL PRODUCT

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

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg losartan potassium and 12.5 mg hydrochlorothiazide.

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. Keep the bottle tightly closed.

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 Comp 100 mg/12.5 mg film-coated tablets blister

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/12.5 mg mg film-coated tablets

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium and 12.5 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Lactose-monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14, 15, 28, 30, 50, 56, 84, 90, 98, or 280 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 package. 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 Comp 100 mg/12.5 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/12.5 mg

Losartan and hydrochlorothiazide

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 Comp 100 mg/12.5 mg film-coated tablets HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/12.5 mg mg film-coated tablets

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium and 12.5 mg hydrochlorothiazide.

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. Keep the bottle tightly closed.

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 Comp 100 mg/12.5 mg film-coated tablets HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/12.5 mg mg film-coated tablets

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium and 12.5 mg hydrochlorothiazide.

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. Keep the bottle tightly closed.

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 Comp 100 mg/25 mg film-coated tablets blister

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/25 mg mg film-coated tablets

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7, 14, 28, 30, 50, 56, 84, 90, 98, or 280 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 package. 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 Comp 100 mg/25 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/25 mg

Losartan and hydrochlorothiazide

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 Comp 100 mg/25 mg film-coated tablets HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/25 mg mg film-coated tablets

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

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. Keep the bottle tightly closed.

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 Comp 100 mg/25 mg film-coated tablets HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar Comp 100 mg/25 mg mg film-coated tablets

Losartan and hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

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. Keep the bottle tightly closed.

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

COZAAR COMP
film-coated Tablets
losartan potassium and hydrochlorothiazide

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 Comp is and what it is used for
2. Before you take Cozaar Comp
3. How to take Cozaar Comp
4. Possible side effects
5. How to store Cozaar Comp
6. Further information

1. WHAT COZAAR COMP IS AND WHAT IT IS USED FOR

Cozaar Comp is a combination of an angiotensin II receptor antagonist (losartan) and a diuretic (hydrochlorothiazide).

Cozaar Comp is indicated for the treatment of essential hypertension (high blood pressure).

2. BEFORE YOU TAKE COZAAR COMP

Do not take Cozaar Comp

- if you are allergic (hypersensitive) to losartan, hydrochlorothiazide or to any of the other ingredients in this medicine.
- if you are allergic (hypersensitive) to other sulfonamide-derived substances (e. g. other thiazides, some antibacterial drugs such as co-trimoxazole, ask your doctor if you are not sure)
- if you are, think you may be or are planning to become pregnant (see also “Pregnancy and breast-feeding”)
- if you are breast-feeding
- if you have severely impaired liver function
- if you have severely impaired kidney function or your kidneys are not producing any urine.
- if you have low potassium, low sodium or high calcium levels which cannot be corrected by treatment
- if you are suffering from gout

Take special care with Cozaar Comp

- if you have previously suffered from swelling of the face, lips, throat or tongue

- if you take diuretics (water pills)
- if you are on a salt-restricted diet
- if you have or have had severe vomiting and/or diarrhoea
- if you have heart failure
- if you have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant
- if you have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function)
- if you have 'aortic or mitral valve stenosis' (narrowing of the valves of the heart) or 'hypertrophic cardiomyopathy' (a disease causing thickening of heart muscle)
- if you are diabetic
- if you have had gout
- if you have or have had an allergic condition, asthma or a condition that causes joint pain, skin rashes and fever (systemic lupus erythematodus).
- if you have high calcium or low potassium levels or you are on a low potassium diet
- if you need to have an anaesthetic (even at the dentist) or before surgery, or if you are going to have tests to check your parathyroid function, you must tell the doctor or medical staff that you are taking Losartan potassium and Hydrochlorothiazide tablets.
- if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldesterone 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.

Diuretic agents such as the hydrochlorothiazide contained in Cozaar Comp may interact with other medicines. Preparations containing lithium should not be taken with Cozaar Comp without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate if you take potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines, other diuretics ("water tablets"), some laxatives, medicines for the treatment of gout, medicines to control heart rhythm or for diabetes (oral agents or insulins). It is also important for your doctor to know if you are taking other medicines to reduce your blood pressure, steroids, medicines to treat cancer, pain killers, drugs for treatment of fungal infections, or arthritis medicines, resins used for high cholesterol, such as colestyramine, medicines which relax your muscles, sleeping tablets; opioid medicines such as morphine , 'pressor amines' such as adrenaline or other drugs from the same group; (oral agents for diabetes or insulins).

Please also inform your doctor when it is planned to apply iodine contrast media about taking Cozaar Comp.

Taking Cozaar Comp with food and drink

You are advised not to drink alcohol whilst taking these tablets: alcohol and Cozaar Comp tablets may increase each other's effects.
Dietary salt in excessive quantities may counteract the effect of Cozaar Comp tablets.
Cozaar Comp tablets may be taken with or without food.

Pregnancy and breast-feeding

You should not take Cozaar Comp 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 Cozaar Comp, 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 Cozaar Comp if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Use in children and adolescents

There is no experience with the use of Cozaar Comp in children. Therefore, Cozaar Comp should not be given to children.

Use in elderly patients

Cozaar Comp works equally well in and is equally well tolerated by most older and younger adult patients. Most older patients require the same dose as younger patients.

Driving and using machines

When you begin treatment with this medication, you should not perform tasks which may require special attention (for example, driving an automobile or operating dangerous machinery) until you know how you tolerate your medicine.

Important information about some of the ingredients of Cozaar Comp

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

3. HOW TO TAKE COZAAR COMP

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

High Blood Pressure
The usual dose of Cozaar Comp for most patients with high blood pressure is 1 tablet of Cozaar Comp 50 mg/12.5 mg per day to control blood pressure over the 24-hour period. This can be increased to 2 tablets once daily of Losartan / Hydrochlorothiazide 50 mg/12.5 mg Film-Coated Tablets or changed to 1 tablet daily of Losartan / Hydrochlorothiazide 100 mg/25 mg Film-Coated Tablets (a stronger strength) per day. The maximum daily dose is 2 tablets per day of Losartan / Hydrochlorothiazide 50 mg/12.5 mg Film-Coated Tablets or 1 tablet daily of Losartan / Hydrochlorothiazide 100 mg/25 mg Film-Coated Tablets

If you take more Cozaar Comp than you should

In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. Overdosage can cause a drop in blood pressure, palpitations, slow pulse, changes in blood composition, and dehydration.

If you forget to take Cozaar Comp
Try to take Cozaar Comp daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.

4. POSSIBLE SIDE EFFECTS

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

If you experience the following, stop taking Cozaar Comp 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 following side effects have been reported:

Common (affecting less than one person in 10 but more than one person in 100):
- Cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder,
- Diarrhoea, abdominal pain, nausea, indigestion,
- Muscle pain or cramps, leg pain, back pain,
- Insomnia, headache, dizziness,
- Weakness, tiredness, chest pain,
- Increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels.

Uncommon (affecting less than one person in 100 but more than one person in 1,000):
- Anaemia, red or brownish spots on the skin (sometimes especially on the feet, legs, arms and buttocks, with joint pain, swelling of the hands and feet and stomach pain), bruising, reduction in white blood cells, clotting problems and bruising,
- Loss of appetite, increased uric acid levels or frank gout, increased blood sugar levels, abnormal blood electrolyte levels,
- Anxiety, nervousness, panic disorder (recurring panic attacks), confusion, depression, abnormal dreams, sleep disorders, sleepiness, memory impairment,
- Pins and needles or similar sensations, pain in the extremities, trembling, migraine, fainting,
- Blurred vision, burning or stinging in the eyes, conjunctivitis, worsening eyesight, seeing things in yellow,
- Ringing, buzzing, roaring or clicking in the ears,
- Low blood pressure, which may be associated with changes in posture (feeling light-headed or weak when you stand up, angina (chest pain), abnormal heartbeat, cerebrovascular accident (TIA, "mini-stroke"), heart attack, palpitations,
- Inflammation of blood vessels, which is often associated with a skin rash or bruising,
- Sore throat, breathlessness, bronchitis, pneumonia, water on the lungs (which causes difficulty breathing), nosebleed, runny nose, congestion,
- Constipation, wind, stomach upsets, stomach spasms, vomiting, dry mouth, inflammation of a salivary gland, toothache,
- Jaundice (yellowing of the eyes and skin), inflammation of the pancreas,
- Hives, itching, inflammation of the skin, rash, redness of the skin, sensitivity to light, dry skin, flushing, sweating, hair loss,
- Pain in the arms, shoulders, hips, knees or other joints, joint swelling, stiffness, muscle weakness,
- Frequent urination including at night, abnormal kidney function including inflammation of the kidneys, urinary infection, sugar in the urine,
- Decreased sexual appetite, impotence,
- Swelling of the face, fever.

Rare (more than 1 out of 10000 patients and less than 1 out of 1000 patients)
- Hepatitis (inflammation of the liver), abnormal liver function tests

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

5. HOW TO STORE COZAAR COMP

Keep out of the reach and sight of children.

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

Store Cozaar Comp in the original package.
Keep the bottle tightly closed. Keep the blister in the outer carton. 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 Comp contains

The active substances are losartan potassium and hydrochlorothiazide.

Cozaar Comp 50 mg/12.5 mg> contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide as the active ingredients.

Cozaar Comp100 mg/12.5 mg mg contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide as the active ingredients.

Cozaar Comp 100 mg/25 mg> contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide as the active ingredients.

Cozaar Comp 50 mg/12.5 mg, Cozaar Comp 100 mg/12.5 mgand Cozaar Comp 100 mg/25 mg contain the following inactive ingredients:
microcrystalline cellulose, lactose monohydrate, pregelatinized maize starch, magnesium stearate, hydroxypropyl cellulose, hypromellose.

Cozaar Comp 50 mg/12.5 mg contains 4.24 mg (0.108 mEq) of potassium. Cozaar Comp 100 mg/12.5 mg mg and Cozaar Comp 100 mg/25 mg contain 8.48 mg (0.216 mEq) of potassium.

Cozaar Comp 50 mg/12.5 mg and Cozaar Comp 100 mg/25 mg also contain titanium dioxide (E171), quinoline yellow aluminum lake (E104) and carnauba wax (E903).

Cozaar Comp 100 mg/12.5 mg also contain: white color concentrate [or the individual ingredients of the concentrate: hydroxypropyl cellulose (E463), hypromellose (E464) and titanium dioxide (E171)] and carnauba wax (E903).

What Cozaar Comp looks like and contents of the pack

Cozaar Comp 50 mg/12.5 mg is supplied as scored or unscored film-coated tablets.

Cozaar Comp 100 mg/12.5 mg mg is supplied as unscored film-coated tablets.

Cozaar Comp 100 mg/25 mg is supplied as unscored film-coated tablets.

Cozaar Comp is supplied in the following pack sizes:

Cozaar Comp 50 mg/12.5 mg> - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, or 280 tablets. HDPE bottles of 100 tablets.

Cozaar Comp 100 mg/12.5 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 14, 15, 28, 30, 50, 56, 84, 90, 98, 280 tablets. HDPE bottles of 100 tablets.

Cozaar Comp 100 mg/25 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 14, 28, 30, 50, 56, 84, 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>

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

Austria	Cosaar Plus - Filmtabletten
Austria	Fortzaar-Filmtabletten
Belgium	COZAAR PLUS FORTE 100 MG/25 MG
Belgium	COZAAR PLUS 50 MG/12,5 MG
Belgium	LOORTAN PLUS FORTE 100 MG/25 MG
Belgium	LOORTAN PLUS 50 MG/12,5 MG
Bulgaria	Hyzaar
Cyprus	FORTZAAR
Cyprus	HYZAAR
Denmark	Cozaar Comp.
Denmark	Cozaar Comp. Forte
Denmark	Cozaar Comp. 100 mg / 12,5 mg
Denmark	Fortzaar
Estonia	HYZAAR
Estonia	FORTZAAR
Finland	Cozaar Comp
Finland	Cozaar Comp Forte
France	Fortzaar 100 mg/25 mg film-coated tablets
France	Hyzaar 100 mg/25 mg film-coated tablets
France	Fortzaar 50 mg/12,5 mg film-coated tablets
France	Hyzaar 50 mg/12,5 mg film-coated tablets
France	Fortzaar 100 mg/12,5 mg film-coated tablets
Germany	LORZAAR PLUS 50/12,5 mg Filmtabletten
Germany	CARDOPAL PLUS 50/12,5 mg Filmtabletten
Germany	LORZAAR VARIPHARM PLUS 50/12,5 mg Filmtabletten
Germany	FORTZAAR 100/25 mg Filmtabletten
Germany	FORTZAAR VARIPHARM 100/25 mg Filmtabletten
Germany	LORZAAR PLUS forte 100/12,5 mg Filmtabletten
Greece	HYZAAR

Greece	HYZAAR 100/25
Hungary	Hyzaar 50/12.5 mg
Hungary	Hyzaar Forte 100/25 mg
Ireland	‘Cozaar’ Comp 50mg/12.5mg film-coated tablets
Ireland	Cozaar’ Comp 100mg/25mg film-coated tablets
Italy	HIZAAR 50 mg + 12,5 mg compresse rivestite con film
Italy	HIZAAR 100 mg + 25 mg compresse rivestite con film
Italy	FORZAAR 100 mg + 25 mg compresse rivestite con film
Italy	NEO-LOTAN PLUS 50 mg + 12,5 mg compresse rivestite con film
Italy	NEO-LOTAN PLUS 100 mg + 25 mg compresse rivestite con film
Italy	LOSAZID 50 mg + 12,5 mg compresse rivestite con film
Italy	LOSAZID 100 mg + 25 mg compresse rivestite con film
Latvia	HYZAAR 50 mg/12,5 mg;
Latvia	Fortzaar 100 mg/25 mg
Lithuania	FORTZAAR (Losartan/Hydrochlorothiazide)
Lithuania	HYZAAR (Losartan/Hydrochlorothiazide)
Luxembourg	COZAAR PLUS FORTE 100 MG/25 MG
Luxembourg	COZAAR PLUS 50 MG/12,5 MG
Luxembourg	LOORTAN PLUS FORTE 100 mg/25 mg
Luxembourg	LOORTAN PLUS 50 mg/12,5 mg
Malta	"Cozaar Comp" 50/12.5 mg pilloli miksija b’rita
Malta	"Cozaar Comp" 100/25 mg pilloli miksija b’rita
Malta	"Cozaar Comp" 100/12,5 mg pilloli miksija b’rita
Netherlands	Cozaar Plus 100/12,5
Netherlands	Fortzaar 100/25
Netherlands	Hyzaar 50/12,5
Poland	HYZAAR
Poland	HYZAAR FORTE
Portugal	COZAAR Plus
Portugal	FORTZAAR
Portugal	SIAARA
Portugal	LORTAAN Plus
Portugal	Losartan + Hidroclorotiazida Frosst
Romania	HYZAAR® 50 mg/12,5 mg, comprimate filmate
Romania	FORTZAAR® 100/ 25 mg, , comprimate filmate
Slovenia	HYZAAR
Slovenia	FORTZAAR
Spain	Cozaar Plus
Spain	Fortzaar
Sweden	Cozaar Comp 50 mg/12,5 mg filmdragerade tabletter
Sweden	Cozaar Comp 100 mg/12,5 mg filmdragerade tabletter

Sweden	Cozaar Comp Forte 100 mg/25 mg filmdragerade tabletter
United Kingdom	COZAAR-COMP 50/12.5MG FILM COATED TABLETS
United Kingdom	COZAAR-COMP 100/25MG FILM COATED TABLETS
United Kingdom	COZAAR-Comp 100 mg/12.5 mg Film-coated tablets
Iceland	COZAAR-COMP 50/12.5MG
Iceland	COZAAR-COMP Forte
Iceland	COZAAR-COMP 100/12.5MG
Norway	Cozaar Comp
Norway	Cozaar Comp Forte

This leaflet was last approved in