ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM(S), STRENGTH(S), ROUTE(S) OF ADMINISTRATION OF THE MEDICINAL PRODUCT(S), MARKETING AUTHORISATION HOLDER(S) IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Invented name** Losartan potassium	**Strength**	**Pharmaceutical Form**	**Route of administration**	**Content (concentration)**
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6, 1220 Wien, Austria	Cosaar 12,5 mg - Filmtabletten	12,5 mg	Film-coated tablet	Oral use	N/A
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6, 1220 Wien, Austria	Cosaar 50 mg - Filmtabletten	50 mg	Film-coated tablet	Oral use	N/A
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6, 1220 Wien, Austria	Cosaar 100 mg - Filmtabletten	100 mg	Film-coated tablet	Oral use	N/A
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR 100 mg	100 mg	Film-coated tablet	Oral use	N/A
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR 50 mg	50 mg	Film-coated tablet	Oral use	N/A
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR 12,5 mg	12,5 mg	Film-coated tablet	Oral use	N/A
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR CARDIO START	21 X 12,5 mg + 14 X 50 mg	Film-coated tablet	Oral use	N/A
Belgium	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN 100 mg	100 mg	Film-coated tablet	Oral use	N/A
Belgium	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN 50 mg	50 mg	Film-coated tablet	Oral use	N/A
Belgium	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN 12,50 mg	12,5mg	Film-coated tablet	Oral use	N/A

Belgium	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN CARDIO START	21 X 12,5 mg + 14 X 50 mg	Film-coated tablet	Oral use	N/A
Bulgaria	Merck Sharp & Dohme Bulgaria EOOD 55 Nikola Vaptzarov blvd. EXPO 2000, east wing, sections B1 & B2, 1st fl. 1407 Sofia, Bulgaria	Cozaar	50 mg	Film-coated tablet	Oral use	N/A
Cyprus	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	COZAAR	50MG	Film-coated tablet	Oral use	N/A
Cyprus	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	COZAAR	100MG	Film-coated tablet	Oral use	N/A
Czech Republic	Merck Sharp & Dohme BV, Postbus 581, Waarderweg 39, 2003 PC, Haarlem, The Netherlands	COZAAR 12,5mg	12,5 mg	Film-coated tablet	Oral use	N/A
Czech Republic	Merck Sharp & Dohme BV, Postbus 581, Waarderweg 39,2003 PC, Haarlem, The Netherlands	COZAAR 50mg	50 mg	Film-coated tablet	Oral use	N/A
Czech Republic	Merck Sharp & Dohme BV, Postbus 581, Waarderweg 39,2003 PC, Haarlem, The Netherlands	COZAAR 100mg	100 mg	Film-coated tablet	Oral use	N/A
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	Cozaar	12,5 mg	Film-coated tablet	Oral use	N/A
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	Cozaar	50 mg	Filmcoated tablet	Oral use	N/A
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem, The Netherlands	Cozaar	100 mg	Filmcoated tablet	Oral use	N/A

Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	Cozaar Startpakke	12,5 mg + 50 mg	Filmcoated tablet	Oral use	N/A
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn, Estonia	Cozaar	100mg	Film-coated tablet	Oral use	N/A
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn, Estonia	Cozaar	50mg	Film-coated tablet	Oral use	N/A
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn, Estonia	Cozaar 12,5 mg	12,5mg	Film-coated tablet	Oral use	N/A
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	12.5 mg	Film-coated tablet	Oral use	N/A
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	12.5 mg and 50 mg (initiation pack)	Film-coated tablet	Oral use	N/A
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	50 mg	Film-coated tablet	Oral use	N/A
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	100 mg	Film-coated tablet	Oral use	N/A
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08, France	Cozaar 100 mg film-coated tablets	100 mg	Film-coated tablet	Oral use	N/A

France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08, France	Cozaar 50 mg scored coated tablets	50 mg	Scored coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	CARDOPAL START 12,5 mg Filmtabletten	12,5 mg	Film-coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	LORZAAR 100 mg Filmtabletten	100 mg	Film-coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	LORZAAR 50 mg Filmtabletten	50 mg	Film-coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	LORZAAR PROTECT 100 mg Filmtabletten	100 mg	Film-coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	LORZAAR PROTECT 50 mg Filmtabletten	50 mg	Film-coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	LORZAAR START 12,5 mg Filmtabletten	12,5 mg	Film-coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	PINZAAR 100 mg Filmtabletten	100 mg	Film-coated tablet	Oral use	N/A
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar, Germany	PINZAAR 50 mg Filmtabletten	50 mg	Film-coated tablet	Oral use	N/A
Germany	VARIPHARM ARZNEIMITTEL GmbH Lindenplatz 1 85540, Haar, Germany	LORZAAR VARIPHARMSTART 12,5 mg Filmtabletten	12,5 mg	Film-coated tablet	Oral use	N/A
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671, Greece	COZAAR	12.5 mg	Film-coated tablet	Oral use	N/A
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671, Greece	COZAAR	50 mg	Film-coated tablet	Oral use	N/A
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671, Greece	COZAAR	100 mg	Film-coated tablet	Oral use	N/A

Hungary	MSD Hungary Ltd 50, Alkotas str. H-1123 Budapest, Hungary	Cozaar	12,5 mg	Tablets, film-coated	Oral use	N/A
Hungary	MSD Hungary Ltd 50, Alkotas str. H-1123 Budapest, Hungary	Cozaar	50 mg	Tablets, film-coated	Oral use	N/A
Hungary	MSD Hungary Ltd 50, Alkotas str. H-1123 Budapest, Hungary	Cozaar	100 mg	Tablets, film-coated	Oral use	N/A
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU, United Kingdom	COZAAR 50 mg Film-coated Tablets	50 mg	Film-coated tablet	Oral use	N/A
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU, United Kingdom	COZAAR 100 mg Film-coated Tablets	100 mg	Film-coated tablet	Oral use	N/A
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU, United Kingdom	COZAAR 12.5mg Film-coated Tablets	12.5mg	Film-coated tablet	Oral use	N/A
Italy	Merck Sharp & Dohme (Italia) S.p.A. Via G. Fabbroni 6, 00191 Rome, Italy	LORTAAN 50 mg compresse rivestite con film	50 mg	Film-coated tablet	Oral use	N/A
Italy	Merck Sharp & Dohme (Italia) S.p.A. Via G. Fabbroni 6, 00191 Rome, Italy	LORTAAN 12,5 mg compresse rivestite con film	12.5 mg	Film-coated tablet	Oral use	N/A
Italy	Merck Sharp & Dohme (Italia) S.p.A. Via G. Fabbroni 6, 00191 Rome, Italy	LORTAAN 100 mg compresse rivestite con film	100 mg	Film-coated tablet	Oral use	N/A
Italy	Neopharmed SpA Via G. Fabbroni 6, 00191 Rome, Italy	NEO-LOTAN 50 mg compresse rivestite con film	50 mg	Film-coated tablet	Oral use	N/A

Italy	Neopharmed SpA Via G. Fabbroni 6, 00191 Rome, Italy	NEO-LOTAN 12,5 mg compresse rivestite con film	12.5 mg	Film-coated tablet	Oral use	N/A
Italy	Neopharmed SpA Via G. Fabbroni 6, 00191 Rome, Italy	NEO-LOTAN 100 mg compresse rivestite con film	100 mg	Film-coated tablet	Oral use	N/A
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- Viale Shakespeare 47, 00144 Rome, Italy	LOSAPREX 50 mg compresse rivestite con film	50 mg	Film-coated tablet	Oral use	N/A
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- Viale Shakespeare 47, 00144 Rome, Italy	LOSAPREX 12,5 mg compresse rivestite con film	12.5 mg	Film-coated tablet	Oral use	N/A
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- Viale Shakespeare 47, 00144 Rome, Italy	LOSAPREX 100 mg compresse rivestite con film	100 mg	Film-coated tablet	Oral use	N/A
Latvia	SIA Merck Sharp & Dohme Latvia, Latvija; Skanstes street 13, LV-1013, Riga, Latvia	Cozaar 50 mg film-coated tablets	50 mg	Film-coated tablets	Oral use	N/A
Latvia	SIA Merck Sharp & Dohme Latvia, Latvija; Skanstes street 13, LV-1013, Riga, Latvia	Cozaar 100 mg film-coated tablets	100 mg	Film-coated tablets	Oral use	N/A
Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius, Lithuania	Cozaar (Losartan)	12,5 mg	film-coated tablet	oral use	N/A
Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius, Lithuania	Cozaar (Losartan)	50 mg	film-coated tablet	oral use	N/A

Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius, Lithuania	Cozaar (Losartan)	100 mg	film-coated tablet	oral use	N/A
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR 100 mg	100 mg	Film-coated tablet	Oral use	N/A
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR 50 mg	50 mg	Film-coated tablet	Oral use	N/A
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR 12,5 mg	12,5 mg	Film-coated tablet	Oral use	N/A
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 - B-1180 Brussels, Belgium	COZAAR CARDIO START	21 X 12,5 mg + 14 X 50 mg	Film-coated tablet	Oral use	N/A
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN 100 mg	100 mg	Film-coated tablet	Oral use	N/A
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN 50 mg	50 mg	Film-coated tablet	Oral use	N/A
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN 12,50 mg	12,5mg	Film-coated tablet	Oral use	N/A
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 - B-1180 Brussels, Belgium	LOORTAN CARDIO START	21 X 12,5 mg + 14 X 50 mg	Film-coated tablet	Oral use	N/A
Malta	Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	"Cozaar 100 mg" pilloli miksija b'rita	100mg	Film-coated tablet	Oral use	N/A
Malta	Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	"Cozaar 50 mg" pilloli miksija b'rita	50mg	Film-coated tablet	Oral use	N/A

Netherlands	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 50	50 mg	Film-coated tablet	Oral use	N/A
Netherlands	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 100	100 mg	Film-coated tablet	Oral use	N/A
Poland	MSD Polska Sp. z o.o. Chłodna 51 00-867 Warsaw, Poland	COZAAR	12.5 mg	Film-coated tablet	Oral use	N/A
Poland	MSD Polska Sp. z o.o. Chłodna 51 00-867 Warsaw, Poland	COZAAR	50 mg	Film-coated tablet	Oral use	N/A
Poland	MSD Polska Sp. z o.o. Chłodna 51 00-867 Warsaw, Poland	COZAAR	100 mg	Film-coated tablet	Oral use	N/A
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos, Portugal	COZAAR	50 mg	Film-coated tablet	Oral use	N/A
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos, Portugal	COZAAR 100 mg	100 mg	Film-coated tablet	Oral use	N/A
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos, Portugal	COZAAR IC	12.5 mg	Film-coated tablet	Oral use	N/A

Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos, Portugal	COZAAR IC – Titulação	12,5 mg + 50 mg	Film-coated tablet	Oral use	N/A
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora, Portugal	LORTAAN IC	12,5 mg	Film-coated tablet	Oral use	N/A
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora, Portugal	LORTAAN IC-Titulação	12,5 mg + 50 mg	Film-coated tablet	Oral use	N/A
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora, Portugal	LORTAAN	50 mg	Film-coated tablet	Oral use	N/A
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora, Portugal	LORTAAN 100mg	100 mg	Film-coated tablet	Oral use	N/A
Romania	Merck Sharp & Dohme Romania S.R.L. Bucharest Business Park Şos. Bucureşti-Ploieşti, Nr. 1A, Clădirea C1, Etaj 3 Sector 1, Bucureşti, România	COZAAR, comprimate filmate, 50 mg	50 mg	Film-coated tablet	Oral use	N/A
Slovakia	Merck Sharp & Dohme B.V. Waarderweg 39, 2031 BN Haarlem P.O. Box 581, 2003 PC Haarlem The Netherlands	COZAAR 12,5 mg	12,5 mg	Film-coated tablet	Oral use	N/A

Slovakia	Merck Sharp & Dohme B.V. Waarderweg 39, 2031 BN Haarlem P.O. Box 581, 2003 PC Haarlem The Netherlands	COZAAR 50 mg	50 mg	Film-coated tablet	Oral use	N/A
Slovakia	Merck Sharp & Dohme B.V. Waarderweg 39, 2031 BN Haarlem P.O. Box 581, 2003 PC Haarlem The Netherlands	COZAAR 100 mg	100 mg	Film-coated tablet	Oral use	N/A
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenia	Cozaar 12,5 mg filmsko obložene tablete	12,5 mg	Film-coated tablet	Oral use	N/A
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenia	Cozaar 50 mg filmsko obložene tablete	50 mg	Film-coated tablet	Oral use	N/A
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenia	Cozaar 100 mg filmsko obložene tablete	100 mg	Film-coated tablet	Oral use	N/A
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 MADRID, Spain	Cozaar 12,5 mg Inicio	12,5 mg	Film-coated tablet	Oral use	N/A
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 MADRID, Spain	Cozaar 50 mg	50 mg	Film-coated tablet	Oral use	N/A
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 MADRID, Spain	Cozaar 100 mg	100 mg	Film-coated tablet	Oral use	N/A
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 12,5 mg filmdragerade tabletter	12,5 mg	Film-coated tablet	Oral use	N/A

Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 12,5 mg + 50 mg filmdragerade tabletter	12,5 + 50 mg	Film-coated tablet	Oral use	N/A
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 50 mg filmdragerade tabletter	50 mg	Film-coated tablet	Oral use	N/A
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 100 mg filmdragerade tabletter	100 mg	Film-coated tablet	Oral use	N/A
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU, United Kingdom	COZAAR 50 mg FILM-COATED TABLETS	50MG	Film-coated tablet	Oral use	N/A
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU, United Kingdom	COZAAR 100MG FILM-COATED TABLETS	100MG	Film-coated tablet	Oral use	N/A
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	12,5 mg	Film-coated tablet	Oral use	N/A
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	50 mg	Film-coated tablet	Oral use	N/A
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	100 mg	Film-coated tablet	Oral use	N/A
Norway	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	12,5 mg	Film-coated tablet	Oral use	N/A

Norway	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	50 mg	Film-coated tablet	Oral use	N/A
Norway	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	100 mg	Film-coated tablet	Oral use	N/A

ANNEX II

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

COZAAR and associated names (see Annex I) 2.5 mg/ml powder and solvent for oral suspension
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of powder for oral suspension delivers 500 mg of losartan potassium. After reconstitution, each ml suspension contains 2.5 mg of losartan potassium.

One bottle of reconstituted suspension (200 ml) contains 500 mg of losartan potassium.

Excipient:
Each ml suspension contains 0.296 mg methylhydroxybenzoate, 0.041 mg propylhydroxybenzoate, 50.6 mg sorbitol, and 1.275 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for oral suspension.

White to off-white powder.

The solvent is a cloudy, colorless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of essential hypertension in adults and in children and adolescents 6 – 16 years of age.
- Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with Angiotensin-converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility*, especially cough,* or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40 % and should be stabilised under the treatment of the chronic heart failure.
- Reduction in the risk of stroke in adult hypertensive patients with left-ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

4.2 Posology and method of administration

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

Paediatric hypertension

Use in children and adolescents (6 to 16 years):

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

The recommended starting dose in patients >20 to <50 kg is 0.7 mg/kg once daily (up to 25 mg total, in exceptional cases where target doses above 25 mg are required, the maximal dose is 50 mg). Dosage should be adjusted according to blood pressure response.

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

For patients who can swallow tablets, this dosage form is also available.

Paediatric patients
Losartan is not recommended:- for use in children below 6 years old due to insufficient data on safety and/or efficacy in these patient groups.

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

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

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

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

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

Special populations

Use in patients with intravascular volume depletion:
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).
Use in patients with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

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

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

Administration of the oral suspension
Shake the closed bottle of losartan oral suspension well before use. Push the plunger of the dispenser completely down toward the tip of the dispenser. Insert the dispenser into the adapter on the medication bottle until a tight seal is made between the bottle and the adapter. With the dispenser, adapter, and bottle attached, turn the entire assembly upside down. Pull out the plunger to withdraw the medication medicinal product into the dispenser. Return the entire assembly to the upright position. Remove the dispenser and administer the medication. Replace the original cap onto the bottle.

For reconstitution see section 6.6.

Losartan may be administered with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Hypotension and Electrolyte/Fluid Imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used (see section 4.2). This also applies to children 6 to 16 years of age.

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

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

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

Use in pediatric patients with renal impairment

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

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended (see section 4.5).

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

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan 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 medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.
There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

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

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

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

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

Sorbitol/Fructose intolerance
The solvent contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Methylhydroxybenzoate and propylhydroxybenzoate.
May cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen, and amifostine) may increase the risk of hypotension.

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

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

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

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

4.6 Pregnancy and lactation

Pregnancy
The use of losartan is not recommended during the first trimester of pregnancy (see section 4.4). The use of losartan is contraindicated 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 medicinal products. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3).
Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken losartan should be closely observed for hypotension.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines 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

Losartan has been evaluated in clinical studies as follows:
- In controlled clinical trials in approximately 3300 adult patients 18 years of age and older for essential hypertension
- In a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy
- In a controlled clinical trial in approximately 3900 patients 20 years of age and older with chronic heart failure
- In a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older with proteinuria
- In a controlled clinical trial in 177 hypertensive pediatric patients 6 to 16 years of age

In these clinical trials, the most common adverse event was dizziness.

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

Hypertension
In controlled clinical trials of approximately 3300 adult patients 18 years of age and older for essential hypertension with losartan the following adverse events were reported.

Nervous system disorders:
Common: dizziness, vertigo

Uncommon: somnolence, headache, sleep disorders

Cardiac disorder:
Uncommon: palpitations, angina pectoris

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

Gastrointestinal disorders:
Uncommon: abdominal pain, obstipation

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

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5 % of patients in hypertension clinical trials.

Hypertensive patients with left-ventricular hypertrophy
In a controlled clinical trial in 9193 hypertensive patients 55 to 80 years of age with left-ventricular hypertrophy the following adverse events were reported:

Nervous system disorders:
common: dizziness

Ear and labyrinth disorders:
common: vertigo

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

Chronic heart failure
In a controlled clinical trial in approximately 3900 patients 20 years of age and older with cardiac insufficiency the following adverse events were reported:

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

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

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastrointestinal disorders:
uncommon: diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders:

uncommon: urticaria, pruritus, rash

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

Investigations:
uncommon: increase in blood urea, serum creatinine and serum potassium has been reported.

Hypertension and type 2 diabetes with renal disease
In a controlled clinical trial in 1513 type 2 diabetic patients 31 years of age and older with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse reactions which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

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

Investigations:
common: hypoglycaemia, hyperkalaemia

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

Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastrointestinal disorders:
not known: diarrhoea

Muscoskeletal and connective tissue disorders:
not known: back pain

Renal and urinary disorders:
not known: urinary tract infections

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

Investigations:
In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9 % of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4 % of patients treated with placebo

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

Blood and lymphatic system disorders:

not known: Anaemia, thrombocytopenia

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

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastrointestinal disorders:
not known: diarrhoea

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

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

Muscoskeletal and connective tissue disorders:
not known: myalgia, arthralgia

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

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

4.9 Overdose

Symptoms of intoxication
No case of overdose has been reported. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA01

5.1 Pharmacodynamic properties

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

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

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

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

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

Hypertension Studies

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

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

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

LIFE-Study

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

The mean length of follow-up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted

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

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

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

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

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

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

In this study 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether Losartan is superior to captopril in reducing all

cause mortality. The primary endpoint did not show any statistically significant difference between Losartan and captopril in reducing all-cause mortality.

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

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

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

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

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

The European Medicines Agency has deferred the obligation to submit the results of studies with <Cozaar and associated names – See Annex I – To be completed nationally> in one or more subsets of the paediatric population in Hypertension, Proteinuria. See 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes,

haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
microcrystalline cellulose (E460)
lactose monohydrate
pregelatinized maize starch
magnesium stearate (E572)
hydroxypropyl cellulose (E463)
hypromellose (E464)
titanium dioxide (E171)

Solvent
microcrystalline cellulose
carboxymethylcellulose sodium
citric acid anhydrous
purified water
xantham gum (E415)
methylhydroxybenzoate (E218)
sodium phosphate monobasic monohydrate
potassium sorbate (E202)
carrageenan calcium sulfate, trisodium phosphate
flavor berry citrus sweet
glycerin
propylhydroxybenzoate (E216)
sodium citrate anhydrous
saccharin sodium
sorbitol (E420)antifoam AF emulsion (contains water, polydimethylsiloxane, C-14-18, mono- and di-glycerides, polyethylene glucol stearate, and polyethylene glycol.)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After reconstitution: 4 weeks.

6.4 Special precautions for storage

Kit: Do not store above 25°C. Store in the original package.
Store the prepared suspension in a refrigerator at 2-8°C.

6.5 Nature and contents of container

The following components are packed in a kit:

- A single aluminum foil sachet filled with powder containing 500 mg losartan potassium The sachet material consists of the following materials, from outside to inside and product contact layer: PET/Ink/ Adhesive/ Foil/ Adhesive/PE
- a 473 ml white, high-density polyethylene (HDPE) bottle of solvent,
- a 240 ml amber polyethylene terephthalate (PET) bottle with polypropylene child resistant closure for mixing the suspension,
- a 10 ml oral dosing polypropylene syringe packed individually with a low density polyethylene push-in bottle neck adapter (PIBA) in a poly bag.

6.6 Special precautions for disposal and other handling

Losartan suspension is a white to off-white liquid when reconstituted with the supplied solution.

Reconstitution of COZAAR oral suspension [for 200 ml of a 2.5 mg/ml suspension]:
Add 200 ml of solvent to the 240 ml amber polyethylene terephthalate (PET) bottle provided. Before opening the sachet gently tap on the side of the sachet to facilitate transfer of the material. Carefully add the complete contents of the sachet into the PET container bottle containing the solvent, tapping the side of the sachet and inverting as necessary. It is normal to have a small amount of residual powder adhering to the interior surfaces of the sachet. The sachet should NOT be rinsed. Place the screw cap on the bottle and shake the contents well to disperse. After reconstitution, losartan suspension is an off-white liquid. Remove the screw cap, place the push-in bottle neck adaptor on the bottle, and re-cap the bottle. The suspension should be stored in a refrigerator at 2-8ºC for up to 4 weeks. Shake the suspension prior to each use and return promptly to the refrigerator.

Discard the excess solvent not used in the preparation of the suspension.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD month YYYY}>
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton of kit

1. NAME OF THE MEDICINAL PRODUCT

COZAAR and associated names (see Annex I) 2.5 mg/ml powder and solvent for oral suspension
Losartan potassium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of powder for oral suspension contains 500 mg of losartan potassium. After reconstitution, each ml suspension contains 2.5 mg of losartan potassium.

One bottle of reconstituted suspension (200 ml) contains 500 mg of losartan potassium.

3. LIST OF EXCIPIENTS

One ml suspension contains 0.296 mg methylhydroxybenzoate, 0.041 mg propylhydroxybenzoate, 50.6 mg sorbitol,.and 1.275 mg lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for oral suspension.

This pack contains:
- One foil sachet filled with 500 mg losartan potassium powder
- One 473 ml bottle of solvent
- One 240 ml bottle with a child resistant closure for mixing the suspension
- One 10 ml oral dosing syringe
- One push-in bottle adaptor

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

Kit: Do not store above 25°C. Store in the original container.
After reconstitution, store the liquid suspension in a refrigerator (at 2°C - 8°C) for up to 4 weeks.

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

[See Annex I - To be completed nationally]

Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

For Healthcare providers only: See Package Leaflet for instructions on how to prepare Losartan potassium oral suspension. It is normal to have a small amount of residual powder adhering to the interior surfaces of the sachet. The sachet should not be rinsed.

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET POWDER LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COZAAR and associated names (see Annex I) 2.5 mg/ml powder and solvent for oral suspension
Losartan potassium.
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 500 mg losartan potassium

6. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL FOR SOLVENT BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Cozaar and associated names (see Annex I) 2.5 mg/ml powder and solvent for oral suspension
Losartan potassium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

One ml solvent contains 0.296 mg methylhydroxybenzoate, 0.041 mg propylhydroxybenzoate, and 50.6 mg sorbitol.

4. PHARMACEUTICAL FORM AND CONTENTS

473 ml solvent

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 container.

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

[See Annex I - To be completed nationally]

Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

To be prepared by medical or healthcare professionals only. See package leaflet for instructions on how to prepare COZAAR 2.5 mg/ml oral suspension.

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL FOR AMBER BOTTLE FOR ORAL SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

COZAAR and associated names (see Annex I) 2.5 mg/ml powder and solvent for oral suspension
Losartan potassium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml suspension contains 2.5 mg of losartan potassium.

3. LIST OF EXCIPIENTS

One ml suspension contains 0.296 mg methylhydroxybenzoate, 0.041 mg propylhydroxybenzoate, 50.6 mg sorbitol and 1.275 mg lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

200 ml oral suspension

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 container.
After reconstitution, store the liquid suspension in a refrigerator (at 2°C - 8°C) for up to 4 weeks.

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

[See Annex I - To be completed nationally]

Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

COZAAR and associated names (see Annex I) 2.5 mg/ml powder and solvent for oral suspension
[See Annex I – To be completed nationally]

Losartan potassium

Read all of this leaflet carefully before you start taking this medicine

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

In this leaflet:

1. WHAT COZAAR IS AND WHAT IT IS USED FOR

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

COZAAR is used

- to treat patients with high blood pressure (hypertension) in adults and in children and adolescents 6 – 16 years of age.
- to protect the kidney in hypertensive type 2 diabetic patients with laboratory evidence ofimpaired renal function and proteinuria ≥ 0.5 g per day (a condition in which urine contains an abnormal amount of protein).
- to treat patients with chronic heart failure when therapy with specific medicines calledangiotensin-converting-enzyme inhibitors (ACE inhibitors, medicine used to lower highblood pressure) is not considered suitable by your doctor. If your heart failure has beenstabilised with an ACE inhibitor you should not be switched to losartan.
- in patients with high blood pressure and a thickening of the left ventricle, COZAAR has been shown to decrease the risk of stroke (“LIFE indication”).

2. BEFORE YOU TAKE COZAAR

Do not take:

- if you are allergic (hypersensitive) to losartan or to any of its other ingredients,
- if your liver function is severely impaired,
- If you are more than 3 months pregnant. (It is also better to avoid COZAAR in early pregnancy – see Pregnancy and breast-feeding section.)
- if you are breast-feeding (see also "Pregnancy and breast-feeding").

Take special care with COZAAR:

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

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or herbal medicines and natural products.
Take particular care if you are taking the following medicines while under treatment with COZAAR:
- other blood pressure lowering medicines as they may additionally reduce your blood pressure. Blood pressure may also be lowered by one of the following drugs/ class of drugs: tricyclic antidepressants, antipsychotics, baclofene, amifostine.
- medicines which retain potassium or may increase potassium levels (e.g. potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamteren, spironolactone] or heparine),
- non-steroidal anti-inflammatory drugs such as indomethacin, including cox-2-inhibitors (medicines that reduce inflammation, and can be used to help relieve pain), as they may reduce the blood lowering effect of losartan. If your kidney function is impaired, the concomitant use of these medicines may lead to a worsening of the kidney function.

Lithium containing medicines should not be taken in combination with losartan without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

Taking with food and drink
COZAAR may be taken with or without food.

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

Use in children and adolescents
COZAAR has been studied in children. For more information, talk to your doctor.

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

Important information about some of the ingredients of COZAAR
COZAAR contains lactose monohydrate and sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

COZAAR also contains methylhydroxybenzoate and propylhydroxybenzoate, which may cause allergic reactions (possibly delayed).

3. HOW TO TAKE COZAAR

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

Adult Patients with High Blood Pressure
- Treatment usually starts with 50 mg losartan (20 ml of COZAAR suspension) once a day. The maximal blood pressure lowering effect should be reached 3-6 weeks after beginning treatment. - In some patients the dose may later be increased to 100 mg losartan (40 ml of COZAAR suspension) once daily.
If you have the impression that the effect of losartan is too strong or too weak, please talk to your doctor or pharmacist.

Use in children and adolescents (6 to 16 years old)
The recommended starting dose in patients who weigh between 20 and 50 kg is 0.7 mg of losartan per kg of body weight administered once a day (up to 25 mg or 10 ml of COZAAR suspension). The doctor may increase the dose if blood pressure is not controlled.

Adult Patients with high blood pressure and type 2 diabetes
Treatment usually starts with 50 mg losartan (20 ml of COZAAR suspension) once a day. The dose may later be increased to 100 mg losartan (40 ml of COZAAR suspension) once daily depending on your blood pressure response.

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

Adult Patients with Heart Failure
Treatment usually starts with 12.5 mg losartan (5 ml of COZAAR suspension) once a day. Generally, the dose should be increased weekly step-by-step (i.e., 12.5 mg daily during the first week, 25 mg daily during the second week, 50 mg daily during the third week) up to the usual maintenance dose of 50 mg losartan (20 ml of COZAAR suspension) once daily according to your condition.

In the treatment of heart failure, losartan is usually combined with a diuretic (medicine that

increases the amount of water that you pass out through your kidneys) and/or digitalis (medicine that helps to make the heart stronger and more efficient) and/or a beta-blocker.

Dosage in special patient groups

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

HOW TO MEASURE AND GIVE A DOSE OF ORAL SUSPENSION

Always shake <COZAAR>oral suspension well before use!

1. Shake the bottle well before use.
2. Push the plunger of the syringe completely down.
3. Insert the syringe into the adaptor on the medicine bottle until a tight seal is made.

4. With the syringe, adapter, and bottle attached, turn the entire assembly upside down.

5. Pull out the plunger to withdraw the medicine into the syringe.

6. Turn the whole thing to an upright position.
7. Remove the syringe and take the medicine.

8. Replace the screw cap onto the bottle.

If you take more COZAAR than you should
If you accidentally take too much COZAAR oral suspension, contact your doctor immediately. Symptoms of overdose are low blood pressure, increased heartbeat, possibly decreased heartbeat.

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

4. POSSIBLE SIDE EFFECTS

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

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

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

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

The side effects of medicines are classified as follows:

Very Common:	***affects more than 1 user in 10***
Common.	***affects 1 to 10 users in 100***
Uncommon:	***affects 1 to 10 users in 1000***
Rare:	***affects 1 to 10 users I 10000***
Very rare:	***affects less than 1 user in 10000***
Not known:	***frequency can not be estimated from the available data***

The following side effects have been reported with COZAAR:

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

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

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

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

Side effects in children are similar to those seen in adults.

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

5. HOW TO STORE COZAAR

Keep out of the reach and sight of children.

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

Store in the original container.
After reconstitution, store the liquid suspension in a refrigerator (at 2°C - 8°C) for up to 4 weeks.

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

6. FURTHER INFORMATION

What COZAAR contains

The active substance is losartan potassium.
Each sachet contains 500 mg of losartan potassium powder. A medical or healthcare professional/pharmacist mixes each sachet with 200 ml of solvent to create a suspension. One ml of suspension contains 2.5 mg of losartan potassium.

The other ingredients are*:*

Powder
Microcrystalline cellulose (E460), Lactose monohydrate, Pregelatinized maize starch, Magnesium stearate (E572), Hydroxypropyl cellulose (E463), Hypromellose (E464), and titanium dioxide (E171)

Solvent
Microcrystalline cellulose (E460), carboxymethylcellulose sodium, citric acid anhydrous, purified water, xantham gum (E415), methylhydroxybenzoate (E218), sodium phosphate monobasic monohydrate, potassium sorbate, carrageenan calcium sulfate trisodium phosphate, flavor berry citrus sweet, glycerin, propylhydroxybenzoate (E216), sodium citrate anhydrous, saccharin sodium, sorbitol (E420)antifoam Af emulsion (contains water, polydimethylsiloxane, C-14-18, mono- and di-glycerides, polyethylene glucol stearate, and polyethylene glycol).

What COZAAR looks like and contents of the pack

COZAAR powder is a white to off-white powder. After suspension in solvent, COZAAR is an off-white liquid.

COZAAR powder and solvent for oral suspension is packaged in a kit containing:
- One foil sachet filled with powder equal to 500 mg losartan potassium
- One 473 ml bottle of solvent
- One 240 ml bottle with a child resistant closure for mixing the suspension
- One 10 ml oral dosing syringe
- One push-in bottle adaptor

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorized in the Member States of the EEA under the following names:
COZAAR 2.5 mg/ml powder and solvent for oral suspension

Austria, Belgium/Luxembourg, Bulgaria, Cyprus, Germany, Denmark, Estonia, Greece, Finland, France, Hungary, Ireland, Italy, Lithuania, Latvia, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom, Iceland, Norway

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Cut at line ----------

The following information is intended for medical or healthcare professionals only:

Preparation of losartan potassium oral suspension [for 200 ml of a 2.5 mg/ml suspension]:
Add 200 ml of solvent to the 240 ml amber polyethylene terephthalate (PET) bottle provided. Before opening the sachet gently tap on the side of the sachet to facilitate transfer of the material. Carefully add the complete contents of the sachet into the PET container bottle containing the solvent, tapping the side of the sachet and inverting as necessary. It is normal to have a small amount of residual powder adhering to the interior surfaces of the sachet. The sachet should NOT be rinsed. Place the cap on the bottle and shake the contents well to disperse. After reconstitution, losartan suspension is an off-white liquid. Remove the cap, place the push-in bottle neck adaptor on the bottle, and re-cap the bottle. The suspension should be stored in a refrigerator at 2-8ºC for up to 4 weeks. Shake the suspension prior to each use and return promptly to the refrigerator.

Discard the excess solvent not used in the preparation of the suspension.

ANNEX III

CONDITIONS OF THE MARKETING AUTHORISATION

The National Competent Authorities, coordinated by the Reference Member State, shall ensure the following conditions are fulfilled by the Marketing Authorisation Holder:

The Applicant commits to provide the following information to the National Competent Authority of the Reference Member State for evaluation:

- PSUR should be submitted every 6 months for a year. After that year the safety data will be evaluated and it will be decided whether a longer PSUR period is permitted. Safety data should be presented in the PSUR separated by age group and used formulation (e.g. tablets or oral suspension).

- The follow-up measures as set out in the CHMP Assessment Report