ANNEX I

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

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Diovan 80 mg/12,5 mg - Filmtabletten	80 mg / 12.5 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Diovan forte 160 mg/12,5 mg - Filmtabletten	160 mg / 12.5 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Diovan 320 mg /12,5 mg - Filmtabletten	320 mg / 12.5 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Diovan fortissimum 160 mg/25 mg - Filmtabletten	160 mg / 25 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Diovan 320 mg/25 mg - Filmtabletten	320 mg / 25 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Angiosan 80 mg/12,5 mg - Filmtabletten	80 mg / 12.5 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Angiosan forte 160 mg / 12,5 mg - Filmtabletten	160 mg / 12.5 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Angiosan 320 mg /12,5 mg - Filmtabletten	320 mg / 12.5 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Angiosan fortissimum 160/25 mg - Filmtabletten	160 mg / 25 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	valsartan + hydrochlorothiazide	Co-Angiosan 320 mg/25 mg - Filmtabletten	320 mg / 25 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co-Diovane 80/12,5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co-Diovane 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co-Diovane 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co-Diovane 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co-Diovane 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co- Novacard 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co- Novacard 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	valsartan + hydrochlorothiazide	Co- Novacard 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Cyprus	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Cyprus	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Cyprus	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Czech Republic	Novartis s.r.o Nagano III. U Nákladového nádraží 10 130 00 Praha 3 Czech Republic	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Czech Republic	Novartis s.r.o Nagano III. U Nákladového nádraží 10 130 00 Praha 3 Czech Republic	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Czech Republic	Novartis s.r.o Nagano III. U Nákladového nádraží 10 130 00 Praha 3 Czech Republic	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Copenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 80 mg/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Copenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 160 mg/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Copenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 320 mg/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Copenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 160 mg/25 mg	160 mg / 25 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Copenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 320 mg/25 mg	320 mg / 25 mg	film-coated tablets	oral
Estonia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	CO-DIOVAN	80 mg / 12.5 mg	film-coated tablets	oral
Estonia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	CO-DIOVAN	160 mg / 12.5 mg	film-coated tablets	oral
Estonia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	CO-DIOVAN 320 mg/12,5 mg FILM-COATED TABLETS	320 mg / 12.5 mg	film-coated tablets	oral
Estonia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	CO-DIOVAN	160 mg / 25 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Estonia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	CO-DIOVAN 320 mg/25 mg FILM-COATED TABLETS	320 mg / 25 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Diovan Comp 80mg/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Diovan Comp 160mg/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Diovan Comp 320mg/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Diovan Comp 160mg/25	160 mg / 25 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Diovan Comp 320mg/25 mg	320 mg / 25 mg	film-coated tablets	oral
France	Novartis Pharma S.A.S. 2 & 4, rue Lionel Terray 92500 RUEIL-MALMAISON, France	valsartan + hydrochlorothiazide	Cotareg 80mg/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
France	Novartis Pharma S.A.S. 2 & 4, rue Lionel Terray 92500 RUEIL-MALMAISON, France	valsartan + hydrochlorothiazide	Cotareg 160mg/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
France	Novartis Pharma S.A.S. 2 & 4, rue Lionel Terray 92500 RUEIL-MALMAISON, France	valsartan + hydrochlorothiazide	Cotareg 160mg/25 mg	160 mg / 25 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Cordinate plus 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Cordinate plus 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Cordinate plus 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan forte 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan forte 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Cordinate plus forte 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Cordinate plus forte 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	provas 80 comp 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	provas 160 comp 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	provas 320 comp 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	provas 160 maxx 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	provas 320 maxx 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Diovan (80+12,5) mg	80 mg / 12,5 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Diovan (160+12,5) mg	160 mg / 12,5 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Diovan (320+12,5) mg	320 mg / 12,5 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Diovan (160+25) mg	160 mg / 25 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Diovan (320+25) mg	320 mg / 25 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Dalzad (80+12.5) mg	80 mg / 12,5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Dalzad (160+12.5) mg	160 mg / 12,5 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Dalzad (320+12.5) mg	320 mg / 12,5 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Dalzad (160+25) mg	160 mg / 25 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 12th Km Metamorphosis GR-144 51	valsartan + hydrochlorothiazide	Co-Dalzad (320+25) mg	320 mg / 25 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	valsartan + hydrochlorothiazide	Diovan HCT 80/12.5 mg filmtabletta	80 mg / 12.5 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	valsartan + hydrochlorothiazide	Diovan HCT 160/12.5 mg filmtabletta	160 mg / 12.5 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	valsartan + hydrochlorothiazide	Diovan HCT 160/25 mg filmtabletta	160 mg / 25 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 80mg/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 160mg/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 320mg/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 160mg/25 mg	160 mg / 25 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	valsartan + hydrochlorothiazide	Diovan Comp 320mg/25 mg	320 mg / 25 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Diovan 80 mg/12.5 mg film-coated tablets	80 mg / 12.5 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 160 mg/12.5 mg film-coated tablets	160 mg / 12.5 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Diovan 320 mg/12.5 mg film-coated tablets	320 mg / 12.5 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 160 mg/25 mg film-coated tablets	160 mg / 25 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Diovan 320 mg/25 mg film-coated tablets mg	320 mg / 25 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Tareg 80 mg/12.5 mg film-coated tablets	80 mg / 12.5 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Tareg 160 mg/12.5 mg film-coated tablets	160 mg / 12.5 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Tareg 320 mg/12.5 mg film-coated tablets	320 mg / 12.5 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Tareg 160 mg/25 mg film-coated tablets	160 mg / 25 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR	valsartan + hydrochlorothiazide	Co-Tareg 320 mg/25 mg film-coated tablets	320 mg / 25 mg	film-coated tablets	oral
Italy	LPB Istituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio (VA)	valsartan + hydrochlorothiazide	CORIXIL 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Italy	LPB Istituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio (VA)	valsartan + hydrochlorothiazide	CORIXIL 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio (VA)	valsartan + hydrochlorothiazide	Cotareg 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio (VA)	valsartan + hydrochlorothiazide	Cotareg 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Italy	LPB Istituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio (VA)	valsartan + hydrochlorothiazide	CORIXIL 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio (VA)	valsartan + hydrochlorothiazide	Cotareg 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Latvia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Latvia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Latvia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Latvia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Latvia	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan 320/25 mg	320 mg / 25 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan	80 mg / 12.5 mg	film-coated tablets	oral
Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan	160 mg / 12.5 mg	film-coated tablets	oral
Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	valsartan + hydrochlorothiazide	Co-Diovan	160 mg / 25 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan forte 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan forte 320/25 mg	320 mg / 25 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Raapopseweg 1 Postbus 241 NL-6824 DP Arnhem	valsartan + hydrochlorothiazide	Co-Diovan filmomhulde tabletten 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Raapopseweg 1 Postbus 241 NL-6824 DP Arnhem	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Netherlands	Novartis Pharma B.V. Raapopseweg 1 Postbus 241 NL-6824 DP Arnhem	valsartan + hydrochlorothiazide	Co-Diovan 320/12.5	320 mg / 12.5 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Raapopseweg 1 Postbus 241 NL-6824 DP Arnhem	valsartan + hydrochlorothiazide	Co-Diovan 160/25	160 mg / 25 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Raapopseweg 1 Postbus 241 NL-6824 DP Arnhem	valsartan + hydrochlorothiazide	Co-Diovan 320/25	320 mg / 25 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern 0510 Oslo	valsartan + hydrochlorothiazide	Diovan Comp 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern 0510 Oslo	valsartan + hydrochlorothiazide	Diovan Comp 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern 0510 Oslo	valsartan + hydrochlorothiazide	Diovan Comp 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern 0510 Oslo	valsartan + hydrochlorothiazide	Diovan Comp 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern 0510 Oslo	valsartan + hydrochlorothiazide	Diovan Comp 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan (80 + 12.5 mg)	80 mg / 12.5 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan (160 + 12.5 mg)	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan (320 + 12.5 mg)	320 mg / 12.5 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan (160 + 25 mg)	160 mg / 25 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan (320 + 25 mg)	320 mg / 25 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Diovan	80/12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Diovan	320 mg / 12.5 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Angiosan	80 mg / 12.5 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Angiosan	160 mg / 12.5 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Angiosan	320 mg / 12.5 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Novasan	80 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Novasan	160 mg / 12.5 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Novasan	320 mg / 12.5 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Diovan Forte	160 mg/25 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Diovan Forte	320 mg / 25 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Angiosan Forte	160 mg / 25 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Angiosan Forte	320 mg / 25 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Novasan Forte	160 mg / 25 mg	film-coated tablets	oral
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edificio 8 Quinta da Beloura P-2710-444 Sintra	valsartan + hydrochlorothiazide	Co-Novasan Forte	320 mg / 25 mg	film-coated tablets	oral
Romania	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 80 mg/12.5 mg, comprimate filmate	80 mg / 12.5 mg	film-coated tablets	oral
Romania	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160 mg/12.5 mg, comprimate filmate	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Romania	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160 mg/25 mg, comprimate filmate	160 mg / 25 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 320/12.5 mg	320 mg / 12.5 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	valsartan + hydrochlorothiazide	Co-Diovan 320/25 mg	320 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Diován 80mg/12.5 mg comprimidos recubiertos con película	80 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Diován 160mg/12.5 comprimidos recubiertos con película mg	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Diován 320/12.5 mg comprimidos recubiertos con películamg	320 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Angiosán 80mg/12.5 mg comprimidos recubiertos con película	80 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Angiosán 160mg/12.5 mg comprimidos recubiertos con película	160 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Angiosán 320mg/12.5 mg comprimidos recubiertos con película	320 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Kalpress Plus 80mg/12.5 mg comprimidos recubiertos con película	80 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Kalpress Plus 160mg/12.5 mg comprimidos recubiertos con película	160 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Kalpress Plus 320mg/12.5 mg comprimidos recubiertos con película	320 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Miten Plus 80mg/12.5 mg comprimidos recubiertos con película	80 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Miten Plus 160mg/12.5 mg comprimidos recubiertos con película	160 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Miten Plus 320mg/12.5 mg comprimidos recubiertos con película	320 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Novasán 80mg/12.5 mg comprimidos recubiertos con película	80 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Novasán 160mg/12.5 mg comprimidos recubiertos con película	160 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Novasán 320mg/12.5 mg comprimidos recubiertos con película	320 mg / 12.5 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Diován Forte 160mg/25 mg comprimidos recubiertos con película	160 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Diován Forte 320mg/25 mg comprimidos recubiertos con película	320 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Angiosán Forte 160mg/25 mg comprimidos recubiertos con película	160 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Angiosán Forte 320mg/25 mg comprimidos recubiertos con película	320 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Kalpress Plus Forte 160mg/25 mg comprimidos recubiertos con película	160 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Kalpress Plus Forte 320mg/25 mg comprimidos recubiertos con película	320 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Miten Plus Forte 160mg/25 mg comprimidos recubiertos con película	160 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Miten Plus Forte 320mg/25 mg comprimidos recubiertos con película	320 mg / 25 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Novasán Forte 160mg/25 mg comprimidos recubiertos con película	160 mg / 25 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 E-08013 Barcelona	valsartan + hydrochlorothiazide	Co-Novasán Forte 320mg/25 mg comprimidos recubiertos con película	320 mg / 25 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Diovan Comp	80 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Diovan Comp	160 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Diovan Comp	320 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Angiosan Comp	80 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby Sverige AB	valsartan + hydrochlorothiazide	Angiosan Comp	160 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Angiosan Comp	320 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Valsartan / Hydroklortiazid Novartis	80 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Valsartan / Hydroklortiazid Novartis	160 mg / 12.5 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Valsartan / Hydroklortiazid Novartis	320 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name** **Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Diovan Comp	160 mg / 25 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Diovan Comp	320 mg / 25 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Angiosan Comp	160 mg / 25 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Angiosan Comp	320 mg / 25 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Valsartan / Hydroklortiazid Novartis	160 mg / 25 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Box 1150 SE-183 11 Täby	valsartan + hydrochlorothiazide	Valsartan / Hydroklortiazid Novartis	320 mg / 25 mg	film-coated tablets	oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Trading as Ciba Laboratories Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 80/12.5 mg	80 mg / 12.5 mg	film-coated tablets	oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Trading as Ciba Laboratories Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 160/12.5 mg	160 mg / 12.5 mg	film-coated tablets	oral

Member State EU / EEA	**Marketing Authorisation**	**INN**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
United Kingdom	Novartis Pharmaceuticals UK Ltd Trading as Ciba Laboratories Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	valsartan + hydrochlorothiazide	Co-Diovan 160/25 mg	160 mg / 25 mg	film-coated tablets	oral

ANNEX II

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

SCIENTIFIC CONCLUSIONS

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

Diovan Comp contains valsartan and hydroclortiazide. Valsartan is an orally active angiotensin II receptor blocker (ARB) and hydrochlorothiazide (HCTZ) is a diuretic. The combination is useful in patients whose blood pressure is not adequately controlled by valsartan monotherapy.
A number of areas of disharmony in the product information for Diovan have been considered by the CHMP.

Section 4.1 – Therapeutic Indications (See Annex III for the agreed therapeutic indications)

"Treatment of essential hypertension in adults"
The data from the 2 factorial and 6 non-responders phase III clinical trials, demonstrate that valsartan administered in combination with HCTZ is effective in reducing BP in patients with essential hypertension without any added concern for safety and tolerability. The efficacy of valsartan/HCTZ was maintained long-term (1-3 yrs) with no significant adverse events being observed compared to short-term therapy. The combination of valsartan/HCTZ was generally well-tolerated and the adverse event and adverse drug reaction profiles were consistent with the pharmaceutical class. Also, the safety profile of the components could be considered well known. In conclusion, the CHMP recommended, in line with the recently finalized referral procedure for Cozaar Comp, that "angiotensin-II-antagonist" is changed to "valsartan" in this indication.
The CHMP adopted the following:
"Diovan Comp fixed dose-combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorotiazide monotherapy"

Section 4.2 - Posology and Method of Administration

Under this section the CHMP identified several area of disagreement.

The first area of disagreement regards the proposal to adapt the posology for the higher dose strengths emphasizing that when a direct switch is made this should only be done in those patients who are on valsartan monotherapy. The data from the two factorial trials and the "Guidance on Clinical Investigation of Medicinal Products in the treatment of hypertension" support the direct change from monotherapy to the fixed combination of 160/25 mg or 320/12.5-25 mg in patients whose blood pressure is not adequately controlled on either valsartan or hydrochlorothiazide monotherapy.
The CHMP finding a little rationale to support this proposal of switch from HCTZ monotherapy to a combination therapy containing 160 or 320 mg of valsartan, found preferable a step-wise dose titration.
The second issue raised in the LoOI was about the step titration. Since a proportion of patients might achieve blood pressure control by only increasing one of the components, and considering a safety issue, with regards to ADR allowing dose titration with both components, the CHMP recommended the titration of only one component at the same time.
The CHMP adopted the following:
"The recommended dose of Diovan Comp X mg/Y mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In each case, up- titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.
The clinical response to Diovan Comp should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Diovan Comp 320 mg/25 mg"

The third issue was discussed that the current MRP SPC restricts the use of both valsartan/HCTZ 160/25 and 320/25 mg to patients whose mean sitting diastolic blood pressure (MSDBP) is ≥100 mmHg. But according to the European hypertension treatment Guidelines (Mancia et al., Eur Heart J 2007;28(12):1462-536) it is no longer warranted. Also, should be taken into account the overall favourable benefit/risk profile of the valsartan/HCTZ 160/25 and 320/25 mg.
In order to evaluate a possible removal of the current restriction the CHMP assessed efficacy and safety data from a sub-group analyses in patients with baseline MSDBP < 100 mmHg and MSDBP ≥100 mmHg. The CHMP, noting that the treatment effects in patients with the higher baseline blood pressure were greater, concluded that a restriction of the use of valsartan/HCTZ 160/25 and 320/25 mg to patients with severely elevated blood pressure is not anymore warranted.

The fourth issue was regarding the time of maximal effects. The CHMP agreed that a greater reduction in both systolic and diastolic BP were seen in the non-responder studies for all strengths from week 4 to week 8 compared to the factorial studies.
Clinical data, however, demonstrate that the antihypertensive effect of all doses of valsartan/HCTZ is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. To support this evidence two studies were submitted: the Placebo-controlled studies and the non-Responder to Valsartan Monotherapy Trials.
In conclusion, the CHMP agreed the following: "*The antihypertensive effect is substantially present within 2 weeks. In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration"*.
Regarding the highest dose only, the CHMP agreed the following:
"If no relevant additional effect is seen with Diovan Comp 320 mg/25 mg after 8 weeks, treatment with an additional or alternative antihypertensive medicinal product should be considered (see section 5.1)".

Regarding *Hepatic impairment* the majority of valsartan is eliminated, mainly as unchanged drug in the bile, by hepatic clearance. Considering that valsartan should not be administered in patients with severe hepatic impairment, biliary cirrhosis and cholestasis, the CHMP recommended to incorporate cross-references to sections 4.3, 4.4 and 5.2.

Section 4.3 – Contraindications

There were significant divergences in the contraindications.
The following contra-indications were not included in all Member States:
- *Hepatic encephalopathy*
- *Biliary obstruction*
- *Gout*
-*Addison's disease*

These contraindications were deleted in the revised PI as the CHMP found enough justifications and agreed about the four exclusion.

Regarding the use of Diovan Comp during pregnancy and lactation, the CHMP decided to delete lactation as a contraindication in the revised SPC.
The AIIR (angiotensin II receptor) antagonists should not be contraindicated during breast-feeding. Although hydrochlorthiazide is excreted into human milk, this does not warrant a contraindication.

Section 4.4 - Special Warnings and Precautions for Use

Regarding the Sodium and/or volume-depleted patients, the CHMP agreed to delete the last sentence of this paragraph considering this was textbook knowledge: *"Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular weakness, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting"*

The CHMP recommended to insert “photosensitivity with hydrochlorothiazide” under this section with a cross reference to section 4.8 and a specific warning for the investigation of parathyroid function. A specific warning for athletes was to be deleted as the CHMP considered that drugs should not be taken for sport purposes.

Section 4.5 - Interaction with Other Medicinal Products and Other Forms of Interaction

According with CHMP recommendation, have been included interaction with valsartan and interaction with hydroclortiazide. Also, a paragraph regarding interaction with tetracycline has been deleted.
Regarding the concomitant use of alcohol during administration of Diovan Comp, the statement *potentiation of orthostatic hypotension may occur* was discussed.

The CHMP considered mentioning in this section a text on transporter proteins involved in uptake and elimination of valsartan and hydrochlorothiazide. The MAH justified the choice of not including information on the involvement of transporter proteins in section 4.5 of Diovan Comp SPC, in line with the outcome of the Diovan referral.

The CHMP agreed on including in the harmonised PI interaction of Diovan Comp with: Metformin and iodine contrast agents.

Section 4.6 - Pregnancy and Lactation

A harmonised wording regarding pregnancy across the Angiotensin II Receptor Antagonists (AIIRA) class was introduced in October 2007 (Recommendations from EMEA Pharmacovigilance Working Party regarding the use of ACE inhibitors & AIIRAs in pregnancy). Based on the QRD comments on the Diovan and on the class labelling text regarding the use of AIIRAs during pregnancy the section 4.6 was implemented.
The CHMP, in the interest of readability, revised this section and agreed on including information about the thiazide.

Section 4.8 - Undesirable Effects

The CHMP agreed including the ADR *Renal failure* as listed in the SPC of Diovan. The inclusion of *syncope* in section 4.8 is also justified. According to “Guideline on SPCs”, the CHMP placed ADR syncope in the frequency category “not known”.

GROUNDS FOR AMENDMENT OF THE SUMMARYOF 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 has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisation for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Diovan 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

Diovan Comp and associated names (see Annex I) 80 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 160 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 160 mg/25 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 320 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 320 mg/25 mg film-coated tablets
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of valsartan and 12.5 mg of hydrochlorothiazide.
Each tablet contains 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.
Each tablet contains 160 mg of valsartan and 25 mg of hydrochlorothiazide.
Each tablet contains 320 mg of valsartan and 12.5 mg of hydrochlorothiazide.
Each tablet contains 320 mg of valsartan and 25 mg of hydrochlorothiazide.

For a full list of excipients, see section 6.1.
[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Diovan Comp fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration

Posology

The recommended dose of Diovan Comp X mg/Y mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.

The clinical response to Diovan Comp should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Diovan Comp 320 mg/25 mg.

The antihypertensive effect is substantially present within 2 weeks.
In most patients, maximal effects are observed within 4 weeks. However, in some patients 4-8 weeks treatment may be required. This should be taken into account during dose titration.

If no relevant additional effect is seen with Diovan Comp 320 mg/25 mg after 8 weeks, treatment with an additional or alternative antihypertensive medicinal product should be considered (see section 5.1).

Method of administration
Diovan Comp can be taken with or without food and should be administered with water.

Special populations

Renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 ml/min). Due to the hydrochlorothiazide component, Diovan Comp is contraindicated in patients with severe renal impairment (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see section 4.4). Diovan Comp is contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly
No dose adjustment is required in elderly patients.

Paediatric patients
Diovan Comp is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
- Second and third trimester of pregnancy (section 4.4 and 4.6).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance <30 ml/min), anuria.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.

4.4 Special warnings and precautions for use

Serum electrolyte changes
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients

Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.

In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Diovan Comp. Sodium and/or volume depletion should be corrected before starting treatment with Diovan Comp.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of Diovan Comp in patients with severe chronic heart failure has not been established.
Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of Diovan Comp as well may be associated with impairment of the renal function. Diovan Comp should not be used in these patients.

Renal artery stenosis
Diovan Comp should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Diovan Comp as their renin-angiotensin system is not activated.

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

Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥30 ml/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Diovan Comp is used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of Diovan Comp in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Diovan Comp should be used with caution (see sections 4.2 and 5.2).

Systemic lupus erythematosus
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.
Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia

may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs 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 AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

General
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to both valsartan and hydrochlorothiazide

Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Other antihypertensive agents
Diovan Comp may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta blockers, calcium channel blockers).

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

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Diovan Comp and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan

Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the hydrochlorothiazide component of Diovan Comp (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide

Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives)
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes
- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine i.v.)

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects favouring the onset of digitalis-induced cardiac arrhythmias.

Calcium salts and vitamin D
Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

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

Beta blockers and diazoxide
Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

Amantadine
Thiazides, including hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine.

Cholestyramine and cholestipol resins
Absorption of thiazide diuretics, including hydrochlorothiazide, is impaired in the presence of anionic exchange resins.

Cytotoxic agents (e.g. cyclophosamide, methotrexate)
Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)
Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

Ciclosporin
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Alcohol, anaesthetics and sedatives
Potentiation of orthostatic hypotension may occur.

Methyldopa
There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

Carbamazepine
Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

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.

4.6 Pregnancy and lactation

Pregnancy

Valsartan

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4).The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 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 AIIRAs 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 AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs 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 AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Lactation
No information is available regarding the use of valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore the use of Diovan Comp during breast feeding is not recommended. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effect of Diovan Comp on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Adverse reactions reported in clinical trials and laboratory findings occurring more frequently with valsartan plus hydrochlorothiazide versus placebo and individual postmarketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been seen in clinical trials may occur during treatment with valsartan/hydrochlorothiazide.

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1. Frequency of adverse reactions with valsartan/hydrochlorothiazide

Metabolism and nutrition disorders	
Uncommon	Dehydration
Nervous system disorders	
Very rare	Dizziness
Uncommon	Paraesthesia
Not known	Syncope
Eye disorders	
Uncommon	Vision blurred
Ear and labyrinth disorders	
Uncommon	Tinnitus
Vascular disorders	
Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	

Uncommon	Cough
Not known	Non cardiogenic pulmonary oedema
Gastrointestinal disorders	
Very rare	Diarrhoea
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Very rare	Arthralgia
Renal and urinary disorders	
Not known	Impaired renal function
General disorders and administration site conditions	
Uncommon	Fatigue
Investigations	
Not known	Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

Additional information on the individual components

Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Diovan Comp as well, even if not observed in clinical trials or during postmarketing period.

Table 2. Frequency of adverse reactions with valsartan

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia
Immune system disorders	
Not known	Other hypersensitivity/allergic reactions including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepatobiliary disorders	
Not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Not known	Angioedema, rash, pruritus
Renal and urinary disorders	
Not known	Renal failure

Table 3: Frequency of adverse reactions with hydrochlorothiazide

Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Diovan Comp. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

Blood and lymphatic system disorders	
Rare	Thrombocytopenia sometimes with purpura
Very rare	Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow depression
Immune system disorders	
Very rare	Hypersenstivity reactions

Psychiatric disorders	
Rare	Depression, sleep disturbances
Nervous system disorders	
Rare	Headache
Cardiac disorders	
Rare	Cardiac arrhythmias
Vascular disorders	
Common	Postural hypotension
Respiratory, thoracic and mediastinal disorders	
Very rare	Respiratory distress including pneumonitis and pulmonary oedema
Gastrointestinal disorders	
Common	Loss of appetite, mild nausea and vomiting
Rare	Constipation, gastrointestinal discomfort
Very rare	Pancreatitis
Hepatobiliary disorders	
Rare	Intrahepatic cholestasis or jaundice
Skin and subcutaneous tissue disorders	
Common	Urticaria and other forms of rash
Rare	Photosensitisation
Very rare	Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
Reproductive system and breast disorders	
Common	Impotence

4.9 Overdose

Symptoms
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.
If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly.
Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, valsartan and diuretics; ATC code: C09D A03.

Valsartan/hydrochlorothiazide
In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (14.9/11.3 mmHg) compared to hydrochlorothiazide 12.5 mg (5.2/2.9 mmHg) and hydrochlorothiazide 25 mg

(6.8/5.7 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (60%) compared to hydrochlorothiazide 12.5 mg (25%) and hydrochlorothiazide 25 mg (27%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 80 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (9.8/8.2 mmHg) compared to valsartan 80 mg (3.9/5.1 mmHg) and valsartan 160 mg (6.5/6.2 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (51%) compared to valsartan 80 mg (36%) and valsartan 160 mg (37%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (16.5/11.8 mmHg) compared to placebo (1.9/4.1 mmHg) and both hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg) and valsartan 80 mg (8.8/8.6 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (64%) compared to placebo (29%) and hydrochlorothiazide (41%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (12.4/7.5 mmHg) compared to hydrochlorothiazide 25 mg (5.6/2.1 mmHg). In addition, a significantly greater percentage of patients responded (BP <140/90 mmHg or SBP reduction ≥20 mmHg or DBP reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/12.5 mg (50%) compared to hydrochlorothiazide 25 mg (25%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 160 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 160/25 mg (14.6/11.9 mmHg) and valsartan/hydrochlorothiazide 160/12.5 mg (12.4/10.4 mmHg) compared to valsartan 160 mg (8.7/8.8 mmHg). The difference in BP reductions between the 160/25 mg and 160/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (68%) and 160/12.5 mg (62%) compared to valsartan 160 mg (49%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) compared to placebo (1.9/4.1 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg), hydrochlorothiazide 25 mg (12.7/9.3 mmHg) and valsartan 160 mg (12.1/9.4 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (81%) and valsartan/ hydrochlorothiazide 160/12.5 mg (76%) compared to placebo (29%) and the respective monotherapies, i.e. hydrochlorothiazide 12.5 mg (41%), hydrochlorothiazide 25 mg (54%), and valsartan 160 mg (59%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (12.4/7.5 mmHg) compared to hydrochlorothiazide 25 mg (5.6/2.1 mmHg). In addition, a significantly greater percentage of patients responded (BP <140/90 mmHg or SBP reduction ≥20 mmHg or DBP reduction

≥10 mmHg) with valsartan/hydrochlorothiazide 160/12.5 mg (50%) compared to hydrochlorothiazide 25 mg (25%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 160 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 160/25 mg (14.6/11.9 mmHg) and valsartan/hydrochlorothiazide 160/12.5 mg (12.4/10.4 mmHg) compared to valsartan 160 mg (8.7/8.8 mmHg). The difference in BP reductions between the 160/25 mg and 160/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (68%) and 160/12.5 mg (62%) compared to valsartan 160 mg (49%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) compared to placebo (1.9/4.1 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg), hydrochlorothiazide 25 mg (12.7/9.3 mmHg) and valsartan 160 mg (12.1/9.4 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (81%) and valsartan/ hydrochlorothiazide 160/12.5 mg (76%) compared to placebo (29%) and the respective monotherapies, i.e. hydrochlorothiazide 12.5 mg (41%), hydrochlorothiazide 25 mg (54%), and valsartan 160 mg (59%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 320 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 320/25 mg (15.4/10.4 mmHg) and valsartan/hydrochlorothiazide 320/12.5 mg (13.6/9.7 mmHg) compared to valsartan 320 mg (6.1/5.8 mmHg).
The difference in systolic BP reduction between the 320/25 mg and 320/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (75%) and 320/12.5 mg (69%) compared to valsartan 320 mg (53%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 320/12.5 mg (21.7/15.0 mmHg) and 320/25 mg (24.7/16.6 mmHg) compared to placebo (7.0/5.9 mmHg) and the respective monotherapies, i.e. hydrochlorothiazide 12.5 mg (11.1/9.0 mmHg), hydrochlorothiazide 25 mg (14.5/10.8 mmHg) and valsartan 320 mg (13.7/11.3 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (85%) and 320/12.5 mg (83%) compared to placebo (45%) and the respective monotherapies, i.e. hydrochlorothiazide 12.5 mg (60%), hydrochlorothiazide 25 mg (66%), and valsartan 320 mg (69%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 320 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 320/25 mg (15.4/10.4 mmHg) and valsartan/hydrochlorothiazide 320/12.5 mg (13.6/9.7 mmHg) compared to valsartan 320 mg (6.1/5.8 mmHg).
The difference in systolic BP reduction between the 320/25 mg and 320/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (75%) and 320/12.5 mg (69%) compared to valsartan 320 mg (53%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 320/12.5 mg (21.7/15.0 mmHg) and 320/25 mg (24.7/16.6 mmHg) compared to placebo (7.0/5.9 mmHg) and the respective monotherapies, i.e. hydrochlorothiazide 12.5 mg (11.1/9.0 mmHg), hydrochlorothiazide 25 mg (14.5/10.8 mmHg) and valsartan 320 mg (13.7/11.3 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (85%) and 320/12.5 mg (83%) compared to placebo (45%) and the respective monotherapies, i.e. hydrochlorothiazide 12.5 mg (60%), hydrochlorothiazide 25 mg (66%), and valsartan 320 mg (69%).

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

Beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular mortality and morbidity are currently unknown.
Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

Valsartan
Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P < 0.05$).

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate. In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4–6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2–4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.
In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE

was reduced (p <0.001) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups. The Diovan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomised to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

Hydrochlorothiazide
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na^+Cl^- symporter perhaps by competing for the Cl^- site, thereby affecting electrolyte reabsorption mechanisms:directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so with co-administration of valsartan the reduction in serum potassium is less pronounced as observed under monotherapy with hydrochlorothiazide.

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide
The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have shown a clear anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo.

Valsartan
Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution
The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation
Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination
Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug.

Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2 h), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily.

Distribution
The distribution and elimination kinetics have generally been described by a bi-exponential decay function. The apparent volume of distribution is 4–8 l/kg.
Circulating hydrochlorothiazide is bound to serum proteins (40–70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 1.8 times the level in plasma.

Elimination
For hydrochlorotiazide, >95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule. The terminal half-life is 6-15 h.

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.
Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal impairment
At the recommended dose of Diovan Comp no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min.

In patients with severe renal impairment (creatinine clearance <30 ml/min) and patients undergoing dialysis no data are available for Diovan Comp. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide (see section 4.3).

Hepatic impairment
In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately 2-fold compared with healthy volunteers.
There is no data available on the use of valsartan in patients with severe hepatic dysfunction (see section 4.3). Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data

The potential toxicity of the valsartan - hydrochlorothiazide combination after oral administration was investigated in rats and marmosets in studies lasting up to six months. No findings emerged that would exclude the use of therapeutic doses in man.

The changes produced by the combination in the chronic toxicity studies are most likely to have been caused by the valsartan component. The toxicological target organ was the kidney, the reaction being more marked in the marmoset than the rat. The combination led to kidney damage (nephropathy with tubular basophilia, rises in plasma urea, plasma creatinine and serum potassium, increases in urine volume and urinary electrolytes from 30 mg/kg/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5-times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m^2 basis. These doses in marmoset, respectively, represent 0.3 and 1.2-times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

High doses of the valsartan - hydrochlorothiazide combination caused falls in red blood cell indices (red cell count, haemoglobin, haematocrit, from 100 + 31 mg/kg/d in rats and 30 + 9 mg/kg/d in marmosets). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m^2 basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

In marmosets, damage was observed in the gastric mucosa (from 30 + 9 mg/kg/d). The combination also led in the kidney to hyperplasia of the afferent aterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m^2 basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

The above mentioned effects appear to be due to the pharmacological effects of high valsartan doses (blockade of angiotensin II-induced inhibition of renin release, with stimulation of the renin-producing cells) and also occur with ACE inhibitors. These findings appear to have no relevance to the use of therapeutic doses of valsartan in humans.

The valsartan - hydrochlorothiazide combination was not tested for mutagenicity, chromosomal breakage or carcinogenicity, since there is no evidence of interaction between the two substances. However, these tests were performed separately with valsartan and hydrochlorothiazide, and produced no evidence of mutagenicity, chromosomal breakage or carcinogenicity.

In rats, maternally toxic doses of valsartan (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbitsIn embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Diovan Comp and associated names (see Annex I) 80 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 160 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 160 mg/25 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 320 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 320 mg/25 mg film-coated tablets
Valsartan/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 80 mg valsartan and 12.5 mg hydrochlorothiazide.
Each film-coated tablet contains 160 mg valsartan and 12.5 mg hydrochlorothiazide.
Each film-coated tablet contains 160 mg valsartan and 25 mg hydrochlorothiazide.
Each film-coated tablet contains 320 mg valsartan and 12.5 mg hydrochlorothiazide.
Each film-coated tablet contains 320 mg valsartan and 25 mg hydrochlorothiazide.

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

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

[To be completed nationally]

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]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

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]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Diovan Comp and associated names (see Annex I) 80 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 160 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 160 mg/25 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 320 mg/12.5 mg film-coated tablets
Diovan Comp and associated names (see Annex I) 320 mg/25 mg film-coated tablets
Valsartan/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Diovan Comp and associated names (see Annex I) **80 mg/12.5 mg film-coated tablets**
Diovan Comp and associated names (see Annex I) **160 mg/12.5 mg film-coated tablets**
Diovan Comp and associated names (see Annex I) **160 mg/25 mg film-coated tablets**
Diovan Comp and associated names (see Annex I) **320 mg/12.5 mg film-coated tablets**
Diovan Comp and associated names (see Annex I) **320 mg/25 mg film-coated tablets**
[See Annex I - To be completed nationally]
Valsartan/hydrochlorothiazide

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 DIOVAN COMP IS AND WHAT IT IS USED FOR

Diovan Comp film-coated tablets contain two active substances called valsartan and hydrochlorothiazide. Both of these substances help to control high blood pressure (hypertension).
- **Valsartan** belongs to a class of medicines known as “angiotensin II receptor antagonists”, which help to control high blood pressure. Angiotensin II is a substance in the body that causes vessels to tighten, thus causing your blood pressure to increase. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.
- **Hydrochlorothiazide** belongs to a group of medicines called thiazide diuretics (also known as “water tablets”). Hydrochlorothiazide increases urine output, which also lowers blood pressure.

Diovan Comp is used to treat high blood pressure which is not adequately controlled by a single substance alone.

High blood pressure increases the workload of the heart and arteries. If not treated, it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure or kidney failure. High blood pressure increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.

2. BEFORE YOU TAKE DIOVAN COMP

Do not take Diovan Comp:
- if you are allergic (hypersensitive) to valsartan, hydrochlorothiazide, sulphonamide derivatives (substances chemically related to hydrochlorothiazide) or to any of the other ingredients of Diovan Comp.
- if you are **more than 3 months pregnant** (it is also better to avoid Diovan Comp in early

pregnancy – see pregnancy section).
- if you have **severe** liver disease.
- if you have **severe** kidney disease.
- if you are unable to urinate.
- if you are treated with an artificial kidney.
- if the level of potassium or sodium in your blood is lower than normal, or if the level of calcium in your blood is higher than normal despite treatment.
- if you have gout.

If any of the above apply to you, do not take this medicine and speak to your doctor.

Take special care with Diovan Comp
- if you are taking potassium-sparing medicines, potassium supplements, salt substitutes containing potassium or other medicines that increase the amount of potassium in your blood such as heparin. Your doctor may need to check the amount of potassium in your blood regularly.
- if you have low levels of potassium in your blood.
- if you have diarrhoea or severe vomiting.
- if you are taking high doses of water tablets (diuretics).
- if you have severe heart disease.
- if you suffer from a narrowing of the kidney artery.
- if you have recently received a new kidney.
- if you suffer from hyperaldosteronism. This is a disease in which your adrenal glands make too much of the hormone aldosterone. If this applies to you, the use of Diovan Comp is not recommended.
- if you have liver or kidney disease.
- if you have fever, rash and joint pain, which may be signs of systemic lupus erythematosus (SLE, a so-called autoimmune disease).
- if you have diabetes, gout, high levels of cholesterol or fats in your blood.
- if you have had allergic reactions with the use of other blood pressure-lowering agents of this class (angiotensin II receptor antagonists) or if you have allergy or asthma.
- it may cause increased sensitivity of the skin to sun.

The use of Diovan Comp in children and adolescents (below the age of 18 years) is not recommended.

You must tell your doctor if you think you are (or might become) pregnant. Diovan Comp is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

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.

The effect of the treatment can be influenced if Diovan Comp is taken together with certain other medicines. It may be necessary to change the dose, to take other precautions, or in some cases to stop taking one of the medicines. This especially applies to the following medicines:

- lithium, a medicine used to treat some types of psychiatric illness
- medicines that affect or can be affected by potassium blood levels, such as digoxin, a medicine to control the heart rhythm, some antipsychotic medicines
- medicines that may increase the amount of potassium in your blood, such as potassium supplements, potassium-containing salt substitutes, potassium-sparing medicines, heparin
- medicines that may reduce the amount of potassium in your blood, such as corticosteroids, some laxatives

- diuretics (water tablets), medicines for the treatment of gout, such as allopurinol, therapeutic vitamin D and calcium supplements, medicines for the treatment of diabetes (oral agents or insulins)
- other medicines to lower your blood pressure, such as beta blockers or methyldopa, or medicines that tighten your blood vessels or stimulate your heart, such as noradrenaline or adrenaline
- medicines to increase blood sugar levels, such as diazoxide
- medicines to treat cancer, such as methotrexate or cyclophosphamide
- pain killers
- arthritis medicines
- muscle relaxing medicines, such as tubocurarine
- anti-cholinergic medicines, such as atropine or biperiden
- amantadine (a medicine used to prevent influenza)
- cholestyramine and colestipol (medicines used to treat high levels of fats in the blood)
- ciclosporin, a medicine used for organ transplant to avoid organ rejection
- some antibiotics (tetracyclines), anaesthetics and sedatives
- carbamazepine, a medicine used to treat seizure conditions

Taking Diovan Comp with food and drink
You can take Diovan Comp with or without food.
Avoid taking alcohol until you have talked to your doctor. Alcohol may make your blood pressure fall more and/or increase the risk of you becoming dizzy or feeling faint.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

- **You must tell your doctor if you think that you are (or might become) pregnant**

Your doctor will normally advise you to stop taking Diovan Comp before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Diovan Comp. Diovan Comp is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if it is used after the third month of pregnancy.

- **Tell your doctor if you are breast-feeding or about to start breast-feeding**

Diovan Comp is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Before you drive a vehicle, use tools or operate machines or carry out other activities that require concentration, make sure you know how Diovan Comp affects you. Like many other medicines used to treat high blood pressure, Diovan Comp may occasionally cause dizziness and affect the ability to concentrate.

Important information about some of the ingredients of Diovan Comp
[To be completed nationally]

3. HOW TO TAKE DIOVAN COMP

Always take Diovan Comp exactly as your doctor has told you. This will help you to get the best results and lower the risk of side effects. You should check with your doctor or pharmacist if you are not sure.

People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for you to keep your appointments with your doctor even if you are feeling well.

Your doctor will tell you exactly how many tablets of Diovan Comp to take. Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

- The usual dose of Diovan Comp is one tablet per day.
- Do not change the dose or stop taking the tablets without consulting your doctor.
- The medicine should be taken at the same time each day, usually in the morning.
- You can take Diovan Comp with or without food.
- Swallow the tablet with a glass of water.

If you take more Diovan Comp than you should
If you experience severe dizziness and/or fainting, lay down and contact your doctor immediately.
If you have accidentally taken too many tablets, contact your doctor, pharmacist or hospital.

If you forget to take Diovan Comp
If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the dose you missed.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Diovan Comp
Stopping your treatment with Diovan Comp may cause your high blood pressure to get worse. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

These side effects may occur with certain frequencies, which are defined 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 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data

Some side effects can be serious and need immediate medical attention:

You should see your doctor immediately if you experience symptoms of angioedema, such as:
- swollen face, tongue or pharynx
- difficulty in swallowing
- hives and difficulties in breathing

Other side effects include:

Uncommon
- cough
- low blood pressure
- light-headedness

- dehydration (with symptoms of thirst, dry mouth and tongue, infrequent urination, dark colored urine, dry skin)
- muscle pain
- tiredness
- tingling or numbness
- blurred vision
- noises (e.g. hissing, buzzing) in ears

Very rare
- dizziness
- diarrhoea
- joint pain

Not known
- breathing difficulty
- severely decreased urine output
- low level of sodium in the blood (sometimes with nausea, tiredness, confusion, malaise, convulsions)
- low level of potassium in the blood (sometimes with muscle weakness, muscle spasms, abnormal heart rhythm)
- low level of white cells in the blood (with symptoms such as fever, skin infections, sore throat or mouth ulcers due to infections, weakness)
- the level of bilirubin increased in blood (which can, in severe cases, trigger yellow skin and eyes)
- the level of blood urea nitrogen and creatinine increased in blood (which can indicate abnormal kidney function)
- the level of uric acid in blood increased (which can, in severe cases, trigger gout)
- syncope (fainting)

Side effects reported with valsartan or hydrochlorothiazide alone, but not observed with Diovan Comp:

Valsartan

Uncommon
- spinning sensation
- abdominal pain

Not known
- skin rash with or without itching together with some of the following signs or symptoms: fever, joint pain, muscle pain, swollen lymph nodes and/or flu-like symptoms
- rash, purplished-red spots, fever, itching (symptoms of inflammation of blood vessels)
- low level of blood platelets (sometimes with unusual bleeding or bruising)
- high level of potassium in the blood (sometimes with muscle spasms, abnormal heart rhythm)
- allergic reactions (with symptoms such as rash, itching, hives, difficulty breathing or swallowing, dizziness)
- swelling mainly of the face and throat; rash; itching
- elevation of liver function values
- the level of haemoglobin decreased and the percentage of red cells decreased in the blood (which both can, in severe cases, trigger an anaemia).
- kidney failure

Hydrochlorothiazide

Common
- itchy rash and other types of rash
- reduced appetite
- mild nausea and vomiting
- faintness, fainting on standing up
- impotence

Rare
- swelling and blistering of the skin (due to increased sensitivity to sun)
- constipation, discomfort of the stomach or bowels, liver disorders (yellow skin or eyes)
- irregular heart beat
- headache
- sleep disturbances
- sad mood (depression)
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin)

Very rare
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever
- itching or red skin
- blistering of the lips, eyes or mouth
- skin peeling
- fever
- facial rash associated with joint pain
- muscle disorder
- fever (cutaneous lupus erythematosus)
- severe upper stomach pain; lack or low levels of different blood cells
- severe allergic reactions
- difficulty breathing
- lung infection; breathlessness

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.

5. HOW TO STORE DIOVAN COMP

- Keep out of the reach and sight of children.
- Do not use Diovan Comp after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
- [Storage conditions statements-To be completed nationally].
- Do not use any Diovan Comp pack that is damaged or shows signs of tampering.
- 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 Diovan Comp contains

[To be completed nationally]

What Diovan Comp looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

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

[To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]