ANNEX I

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

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Diovan 40 mg Filmtabletten	40 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Angiosan 40 mg Filmtabletten	40 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Diovan 80 mg Filmtabletten	80 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Angiosan 80 mg Filmtabletten	80 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Diovan 160 mg Filmtabletten	160 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Angiosan 160 mg Filmtabletten	160 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Diovan 320 mg Filmtabletten	320 mg	film-coated tablets	oral
Austria	Novartis Pharma GmbH Brunner Strasse 59 A-1235 Wien	Angiosan 320 mg Filmtabletten	320 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Diovane 40 mg	40 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Novacard 40 mg	40 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Diovane 80 mg	80 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Novacard 80 mg	80 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Diovane 160 mg	160 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Novacard 160 mg	160 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Diovane 320 mg	320 mg	film-coated tablets	oral
Belgium	N.V. Novartis Pharma S.A. Medialaan 40, bus 1 B-1800 Vilvoorde	Novacard 320 mg	320 mg	film-coated tablets	oral
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 40 mg	40 mg	film-coated tablets	oral
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 80 mg	80 mg	film-coated tablets	oral
Bulgaria	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 160 mg	160 mg	film-coated tablets	oral
Cyprus	Demetriades & Papaellinas ltd 21 Kasou P.O. Box 23490 Nicosia Cyprus	Diovan 40 mg	40 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Cyprus	Demetriades & Papaellinas ltd 21 Kasou P.O. Box 23490 Nicosia Cyprus	Diovan 80 mg	80 mg	film-coated tablets	oral
Cyprus	Demetriades & Papaellinas ltd 21 Kasou P.O. Box 23490 Nicosia Cyprus	Diovan 160 mg	160 mg	film-coated tablets	oral
Cyprus	Demetriades & Papaellinas ltd 21 Kasou P.O. Box 23490 Nicosia Cyprus	Diovan 320 mg	320 mg	film-coated tablets	oral
Czech Republic	NOVARTIS s.r.o. Pharma Nagano III. U Nákladového nádraží 10 130 00 Praha 3	Diovan 40 mg	40 mg	film-coated tablets	oral
Czech Republic	NOVARTIS s.r.o. Pharma Nagano III. U Nákladového nádraží 10 130 00 Praha 3	Diovan 160 mg	160 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 40 mg	40 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 80 mg	80 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 160 mg	160 mg	film-coated tablets	oral
Denmark	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 320 mg	320 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Estonia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 40 mg	40 mg	film-coated tablets	oral
Estonia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 80 mg	80 mg	film-coated tablets	oral
Estonia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 160 mg	160 mg	film-coated tablets	oral
Estonia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 320 mg	320 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 40 mg	40 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 80 mg	80 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 160 mg	160 mg	film-coated tablets	oral
Finland	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 320 mg	320 mg	film-coated tablets	oral
France	Novartis Pharma S.A.S. 2 and 4, rue Lionel Terray 92500 RUEIL-MALMAISON France	Tareg 40 mg	40 mg	film-coated tablets	oral
France	Novartis Pharma S.A.S. 2 and 4, rue Lionel Terray 92500 RUEIL-MALMAISON France	Tareg 80 mg	80 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France	Novartis Pharma S.A.S. 2 and 4, rue Lionel Terray 92500 RUEIL-MALMAISON France	Tareg 160 mg	160 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 40 mg	40 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Cordinate 40 mg	40 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Provas 40 mg	40 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 80 mg	80 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Cordinate 80 mg	80 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Provas 80 mg	80 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 160 mg	160 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Cordinate 160 mg	160 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Provas 160 mg	160 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 320 mg	320 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Cordinate 320 mg	320 mg	film-coated tablets	oral
Germany	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Provas 320 mg	320 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Diovan 40 mg	40 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Dalzad 40 mg	40 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Diovan 80 mg	80 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Dalzad 80 mg	80 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Diovan 160 mg	160 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis	Dalzad 160 mg	160 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	GR-144 51 Athens				
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Diovan 320 mg	320 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Dalzad 320 mg	320 mg	film-coated tablets	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Diovan 80 mg	80 mg	Hard gelatine capsules	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Dalzad 80 mg	80 mg	Hard gelatine capsules	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Diovan 160 mg	160 mg	Hard gelatine capsules	oral
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens	Dalzad 160 mg	160 mg	Hard gelatine capsules	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Diovan 40 mg	40 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Varexan 40 mg	40 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Diovan 80 mg	80 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Varexan 80 mg	80 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Diovan 160 mg	160 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Varexan 160 mg	160 mg	film-coated tablets	oral
Hungary	Novartis Hungaria Kft. Bartók Béla út 43-47 H-1114 Budapest	Diovan 320 mg	320 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 40 mg	40 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 80 mg	80 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 160 mg	160 mg	film-coated tablets	oral
Iceland	Novartis Healthcare A/S Lyngbyvej 172 DK-2100 Kopenhagen Ø	Diovan 320 mg	320 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 40 mg	40 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 80 mg	80 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 160 mg	160 mg	film-coated tablets	oral
Ireland	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 320 mg	320 mg	film-coated tablets	oral
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Tareg 40 mg	40 mg	film-coated tablets	oral
Italy	LPB Instituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio	Rixil	40 mg	film-coated tablets	oral
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Tareg	80 mg	film-coated tablets	oral
Italy	LPB Instituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio	Rixil	80 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Tareg	160 mg	film-coated tablets	oral
Italy	LPB Instituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio	Rixil	160 mg	film-coated tablets	oral
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Tareg	80 mg	Hard capsules	oral
Italy	LPB Instituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio	Rixil	80 mg	Hard capsules	oral
Italy	Novartis Farma S.p.A. Largo Umberto Boccioni 1 I-21040 Origgio	Tareg	160 mg	Hard capsules	oral
Italy	LPB Instituto Farmaceutico S.r.l. Largo Umberto Boccioni 1 I-21040 Origgio	Rixil	160 mg	Hard capsules	oral
Latvia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 40 mg	40 mg	film-coated tablets	oral
Latvia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 80 mg	80 mg	film-coated tablets	oral
Latvia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 160 mg	160 mg	film-coated tablets	oral
Latvia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 320 mg	320 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 80 mg	80 mg	film-coated tablets	oral
Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 160 mg	160 mg	film-coated tablets	oral
Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo	Diovan 320 mg	320 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 40 mg	40 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 80 mg	80 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 160 mg	160 mg	film-coated tablets	oral
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 320 mg	320 mg	film-coated tablets	oral
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 40 mg	40 mg	film-coated tablets	oral
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 80 mg	80 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 160 mg	160 mg	film-coated tablets	oral
Malta	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 320 mg	320 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Postbus 241 NL-6824 DP Arnhem	Diovan 40	40 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Postbus 241 NL-6800 LZ Arnhem	Diovan 80	80 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Postbus 241 NL-6824 DP Arnhem	Diovan 160	160 mg	film-coated tablets	oral
Netherlands	Novartis Pharma B.V. Postbus 241 NL-6824 DP Arnhem	Diovan 320	320 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern NO-0510 Oslo	Diovan 40 mg	40 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern NO-0510 Oslo	Diovan 80 mg	80 mg	film-coated tablets	oral
Norway	Novartis Norge AS Postboks 237 Økern NO-0510 Oslo	Diovan 160 mg	160 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Norway	Novartis Norge AS Postboks 237 Økern NO-0510 Oslo	Diovan 320 mg	320 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan	40 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan	80 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan	160 mg	film-coated tablets	oral
Poland	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan	320 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	Diovan	40 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	Diovan	80 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	Diovan g	160 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) 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	Diovan	320 mg	film-coated tablets	oral
Romania	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 40 mg	40 mg	film-coated tablets	oral
Romania	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 80 mg	80 mg	film-coated tablets	oral
Romania	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 160 mg	160 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	Diovan 40 mg	40 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	Diovan 80 mg	80 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	Diovan 160 mg	160 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	Diovan 320 mg	320 mg	film-coated tablets	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	Diovan 80 mg	80 mg	Hard gelatine capsules	oral
Slovak Republic	Novartis s.r.o. Prague Czech Republic	Diovan 160 mg	160 mg	Hard gelatine capsules	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 40 mg filmsko obložene tablete	40 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 80 mg filmsko obložene tablete	80 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 160 mg filmsko obložene tablete	160 mg	film-coated tablets	oral
Slovenia	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg	Diovan 320 mg filmsko obložene tablete	320 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Diovan Cardio 40 mg	40 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Kalpress Cardio 40 mg	40 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Miten Cardio 40 mg	40 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Diovan 80 mg	80 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Kalpress 80 mg	80 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Miten 80 mg	80 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Diovan 160 mg	160 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Kalpress 160 mg	160 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Miten 160 mg	160 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Diovan 320 mg	320 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Kalpress 320 mg	320 mg	film-coated tablets	oral
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona	Miten 320 mg	320 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Diovan	40 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Angiosan	40 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Valsartan Novartis	40 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Diovan	80 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Angiosan	80 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Valsartan Novartis	80 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Diovan	160 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Angiosan	160 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Valsartan Novartis	160 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Diovan	320 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Angiosan	320 mg	film-coated tablets	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Valsartan Novartis	320 mg	film-coated tablets	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Diovan	80 mg	Hard gelatine capsules	oral
Sweden	Novartis Sverige AB Kemistvägen 1B P.O. Box 1150 S-183 11 Täby	Diovan	160 mg	Hard gelatine capsules	oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 40 mg	40 mg	film-coated tablets	oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 320 mg	320 mg	film-coated tablets	oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 40 mg	40 mg	Hard gelatine capsules	oral
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 80 mg	80 mg	Hard gelatine capsules	oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
United Kingdom	Novartis Pharmaceuticals UK Ltd Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	Diovan 160 mg	160 mg	Hard gelatine capsules	oral

ANNEX II

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

SCIENTIFIC CONCLUSIONS

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

Diovan contains valsartan, an orally Angiotensin II Receptor Antagonist (AIIRA). Diovan was included in the list of products for Summary of Products Characteristics (SPC) harmonization, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended, as the above-mentioned medicinal product does not have the same SPC across all EU Member States, Iceland and Norway.

Critical Evaluation
A number of areas of disharmony in the product information for Diovan have been evaluated by the CHMP and a revised PI was adopted. The main areas for harmonisation were as follows.

4.1 - Therapeutic Indications

Regarding the indication in hypertension, the CHMP considered that valsartan is an established therapy for hypertension and there is no substantial discrepancy between the national SPCs. The CHMP was also of the opinion that the 320 milligram dose provides a modest, statistically significant additional reduction in MSDBP and MSSBP compared to 160mg and a similarly modest increase in the rate of blood pressure control. The proposed harmonized text for this section is acceptable by the majority of CHMP members in regard to this indication; therefore the following wording was adopted:

"*Treatment of essential hypertension*"

Regarding the indication in recent myocardial infarction the CHMP noted that this indication was limited to patients intolerants to ACE inhibitors in some Member States. The CHMP considered the VALIANT study which demonstrated that valsartan given as monotherapy is at least as effective as captopril given as monotherapy in the reduction of total mortality after an acute myocardial infarction. The results for the pre-specified secondary endpoints support that valsartan is as effective as captopril. Considering the non inferiority in clinical outcome of valsartan compared to current standard treatment, an ACEI, the CHMP adopted the following harmonised wording for this indication:

"Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours – 10 days) myocardial infarction"

The therapeutic indication for heart failure is supported primarily by a large long-term morbidity trial Valsartan Heart Failure Trial (Val-HeFT) Valsartan reduced the risk related to first morbid event, mortality, the total number of Heart Failure (HF) hospitalizations. Valsartan also demonstrated beneficial effects on signs and symptoms of HF. This indication was approved in all Member States and the CHMP adopted the following wording:

"Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors could not be used, or as add-on therapy to ACE inhibitors when beta blockers could not be used"

4.2 - Posology

The first area of disagreement is about the use of triple combination (Valsartan + ACEI+ BB) in chronic HF.
The dosing schedule for the therapeutic use of valsartan in heart failure was based on the Val-HeFT study. In addition the VALIANT study demonstrated that mortality was not increased in patients receiving the triple combination. Therefore in the situation of potential use of the triple combination

the text within the SPC has been adjusted to indicate that caution (rather than "not recommended") is appropriate

The CHMP considered that there is little support for the triple combination use so far. In CHMP's opinion the wording "not recommended" should be used until there is more solid supportive benefit/risk-profile evidence to triple combination. Therefore the MAH should address the lack of (additional) clinical benefit and increased adverse events In conclusion; the CHMP adopts the revised text:
"The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1). Evaluation of patients with heart failure should always include assessment of renal function."

Acknowledging the comments from the CHMP and the Rapporteurs and in the absence of any new data regarding triple therapy with valsartan, the MAH proposed to substitute the wording "the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended" in chronic heart failure as requested in the relevant sections of the SPC (sections 4.2 and 4.4). The CHMP proposed wording has been accepted by the MAH. The issue has been solved

In section 4.2 there are also differences in SPC across Member States in relation to the dosage recommendation in patients with renal and hepatic impairment.

Regarding renal impairment, the use of valsartan 80 mg as the starting dose, with no dosage adjustment, in patients with reduced renal function (creatinine clearance rate >10 ml/min) is supported by both efficacy and safety data from Study 27 and by pharmacokinetic data from Study 12. In Study 27 the kinetic of valsartan was also investigated in hypertensive patients with impairment of renal function (creatine clearance rate: 16-116 mL/min). The CHMP considered that the elimination of valsartan at steady-state is similar in patients with renal impairment when compared with healthy volunteers and adopted the following wording: "*No dosage adjustment is required for patients with a creatinine clearance >10 ml/min."*

Regarding hepatic impairment, the CHMP noted that the majority of valsartan is eliminated, mainly as unchanged drug in the bile, through hepatic clearance. Valsartan does not undergo extensive biotransformation and 70% of the available dose is excreted. The potential for hepatic function per se to affect the kinetics of valsartan is therefore limited, except in the case of biliary obstruction or cholestatic liver disease (defined as an alkaline phosphatase concentration > 2 X Upper Limit of Normal). In Study 46, the exposure to valsartan was determined in patients with mild and moderate impairment of liver function. Exposure to valsartan is not correlated with the degree of liver dysfunction, although the presence of liver disease tended to increase the valsartan plasma AUC. Based on the modest magnitude of the observed increase in AUC, and the wide therapeutic index for valsartan, no initial dose adjustment is considered necessary in patients with mild to moderate impairment of hepatic function (without cholestasis). Based on a pharmacokinetic study, the dose of valsartan should not exceed 80 mg in these patients and should be used with caution. Valsartan should not be administered in patients with severe hepatic impairment, cirrhosis or biliary obstruction. The wording proposed by the MAH in the SPC was acceptable to the CHMP and the following wording was adopted: "*In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see section 4.4)."*

4.3 - Contraindications

There was disagreement on whether the use of Diovan should be contraindicated in patients with renal failure. Having assessed the data available, the CHMP considered that the use of valsartan 80 mg as the starting dose, with no dosage adjustment, in patients with reduced renal function (creatinine

clearance rate >10 ml/min) is supported by both efficacy and safety data from various studies. The safety and tolerability of valsartan in patients with severe renal failure (creatinine clearance of <10 ml/min) was not evaluated in any clinical study. However, no safety issue can be predicted because valsartan would not have specific safety issues associated with renal failure in general.
The CHMP considered it acceptable to remove this contraindication, as the primary route of elimination of valsartan is via biliary route and renal clearance accounts for less than 30% of plasma clearance. Based on this data, the tolerability would be expected to be similar between those two groups.

The CHMP also considered that in view of the fact that Diovan is eliminated via the biliary route, it should be contraindicated in patients with severe liver diseases and "should not be administered in patients with severe hepatic impairment, cirrhosis or biliary obstruction. With reference to the contraindication for the use of Diovan during pregnancy or lactation, the CHMP in line with the recommendations of the Pharmacovigilance experts considered that the contraindication shall be removed and the following recommendation included in the specific section relevant to pregnancy and lactation as follows: *"Because no information is available regarding the use of valsartan during breastfeeding, Diovan (Valsartan) is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant".*

4.5 - Interaction with other medicinal products and other forms of interaction

The CHMP considered the precautions for the concomitant use of other medicinal products containing or raising the level of potassium and adopted the following wording: *"If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised".*

The CHMP also considered that special precaution would be needed for patients with hepatic impairment and/or cholestasis, as the majority of valsartan is eliminated, mainly as unchanged drug in the bile, by hepatic clearance. Based on the wide therapeutic index for valsartan, no initial dose adjustment is considered necessary in patients with mild to moderate impairment of hepatic function (without cholestasis). Based on a pharmacokinetic study, the dose of valsartan should not exceed 80 mg in these patients and should be used with caution.

The CHMP agreed about the proposed wording for precautions in dosing Diovan, considering that no dosage adjustment is required for patients with a creatinine clearance >10ml/min and that in patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see section 4.4).

Sessions 4.5, 5.1, and 5.2 have been updated in order to guarantee the safety of the medicine.
The following sentence has been added to Section 5.2: "*Diovan has not been studied in patients with severe hepatic dysfunction"*. In patients with a creatinine clearance <10 ml/min and patients undergoing dialysis no data are available, therefore valsartan should be used with caution in these patients.

4.8 - Undesirable effect

The main discussion for this section concerned the presentation of ADRs in the SPC. The MAH created a single table containing all relevant ADRs from all three indications: hypertension, post- MI, and CHF. However, the CHMP, requested to summarize all indications in one table, according to the `Guideline of SPC`. The MAH proposed to add indication-specific foot-notes, but the CHMP considered that the proposed extensive use of footnotes has little value for the prescriber and ADRs have been moved to the frequency category representing the highest frequency (see attached SPC and PIL).

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

Whereas

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

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

the CHMP has recommended the amendment of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Diovan 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 and associated names (see Annex I) 40 mg film-coated tablets
Diovan and associated names (see Annex I) 40 mg capsules, hard
Diovan and associated names (see Annex I) 80 mg film-coated tablets
Diovan and associated names (see Annex I) 80 mg capsules, hard
Diovan and associated names (see Annex I) 160 mg film-coated tablets
Diovan and associated names (see Annex I) 160 mg capsules, hard
Diovan and associated names (see Annex I) 320 mg film-coated tablets
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 40 mg of valsartan
One capsule contains 40 mg of valsartan
One film-coated tablet contains 80 mg of valsartan
One capsule contains 80 mg of valsartan
One film-coated tablet contains 160 mg of valsartan
One capsule contains 160 mg of valsartan
One film-coated tablet contains 320 mg of valsartan

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

Recent myocardial infarction
Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction (see sections 4.4 and 5.1).

Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used (see sections 4.4 and 5.1).

Hypertension
Treatment of essential hypertension.

Recent myocardial infarction
Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction (see sections 4.4 and 5.1).

Heart failure
Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used (see sections 4.4 and 5.1).

Hypertension
Treatment of essential hypertension.

4.2 Posology and method of administration

Posology

Recent myocardial infarction
In clinically stable patients, therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.
The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160 mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dosage reduction.
Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins, and diuretics. The combination with ACE inhibitors is not recommended (see sections 4.4 and 5.1).
Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Heart failure
The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1).
Evaluation of patients with heart failure should always include assessment of renal function.

Hypertension
The recommended starting dose of Diovan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.
Diovan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Recent myocardial infarction
In clinically stable patients, therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.
The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160 mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dosage reduction.
Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins, and diuretics. The combination with ACE inhibitors is not recommended (see sections 4.4 and 5.1).
Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Heart failure
The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the

patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1).
Evaluation of patients with heart failure should always include assessment of renal function.

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Diovan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Method of administration
Diovan may be taken independently of a meal and should be administered with water.

Additional information on special populations

Elderly
No dose adjustment is required in elderly patients.

Renal impairment
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min (see sections 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. Diovan is contraindicated in patients with severe hepatic impairment and in patients with cholestasis (see sections 4.3, 4.4 and 5.2).

Paediatric patients
Diovan 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 the active substance or to any of the excipients.
-Severe hepatic impairment, biliary cirrhosis and cholestasis.
-Second and third trimester of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Hyperkalaemia
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.

Sodium- and/or volume-depleted patients
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. Sodium and/or volume depletion should be corrected before starting treatment with Diovan, for example by reducing the diuretic dose.

Renal artery stenosis

In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Diovan has not been established.
Short-term administration of Diovan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

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

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

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

Impaired renal function
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 5.2).

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

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).

Recent myocardial infarction
The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see sections 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.
Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).
Use of Diovan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

Heart Failure
In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and Diovan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended.
Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).

Use of Diovan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).
In patients whose renal function may depend on the activity of the renin-angiotensin 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 and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Diovan may be associated with impairment of the renal function.

Recent myocardial infarction
The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies (see sections 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.
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Use of Diovan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

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In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and Diovan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended.
Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).
Use of Diovan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).
In patients whose renal function may depend on the activity of the renin-angiotensin 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 and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Diovan may be associated with impairment of the renal function.

Other conditions with stimulation of the renin-angiotensin system
In patients whose renal function may depend on the activity of the renin-angiotensin 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 and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Diovan may be associated with impairment of the renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. 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.

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.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of 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.

Others
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, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Pregnancy and lactation

Pregnancy

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the 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 AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with 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, hyperkalemia); see also section 5.3 “Preclinical safety data”.
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 sections 4.3 and 4.4).

Lactation
Because no information is available regarding the use of valsartan during breastfeeding, Diovan is not recommended and 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 effects on the ability to drive 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

In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.
For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

- **Hypertension**

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Elevation of liver function values including increase of serum bilirubin
Skin and subcutaneous tissue disorders	
Not known	Angioedema, Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Elevation of serum creatinine
General disorders and administration site conditions	
Uncommon	Fatigue

The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below:

- **Post-myocardial infarction and/or heart failure**

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia
Not known	Increase of serum potassium
Nervous system disorders	

Common	Dizziness, Postural dizziness
Uncommon	Syncope, Headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, Orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, Diarrhoea
Hepato-biliary disorders	
Not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Rash, Pruritis
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, Elevation of serum creatinine
Not known	Increase in Blood Urea Nitrogen
General disorders and administration site conditions	
Uncommon	Asthenia, Fatigue

4.9 Overdose

Symptoms
Overdose with Diovan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilisation of the circulatory condition is of prime importance.
If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken.
Valsartan is unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03

Valsartan is an orally active, potent, 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) less 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).

Recent myocardial infarction

The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomised, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (manifested as an ejection fraction ≤40% by radionuclide ventriculography or ≤35% by echocardiography or ventricular contrast angiography). Patients were randomised within 12 hours to 10 days after the onset of myocardial infarction symptoms to valsartan, captopril, or the combination of both. The mean treatment duration was two years. The primary endpoint was time to all-cause mortality.

Valsartan was as effective as captopril in reducing all-cause mortality after myocardial infarction. All-cause mortality was similar in the valsartan (19.9%), captopril (19.5%), and valsartan + captopril (19.3%) groups. Combining valsartan with captopril did not add further benefit over captopril alone. There was no difference between valsartan and captopril in all-cause mortality based on age, gender, race, baseline therapies or underlying disease. Valsartan was also effective in prolonging the time to and reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).

The safety profile of valsartan was consistent with the clinical course of patients treated in the post-myocardial infarction setting. Regarding renal function, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan+captopril-treated patients, and 3.4% of captopril-treated patients. Discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients, 1.3% in valsartan+captopril patients, and 0.8% of captopril patients. An assessment of renal function should be included in the evaluation of patients post-myocardial infarction.

There was no difference in all-cause mortality, cardiovascular mortality or morbidity when beta blockers were administered together with the combination of valsartan + captopril, valsartan alone, or captopril alone. Irrespective of treatment, mortality was lower in the group of patients treated with a beta blocker, suggesting that the known beta blocker benefit in this population was maintained in this trial.

Heart failure

Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62%), III (36%) and IV (2%) heart failure patients receiving usual therapy with LVEF <40% and left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m^2. Baseline therapy included ACE inhibitors (93%), diuretics (86%), digoxin (67%) and beta blockers (36%). The mean duration of follow-up was nearly two years. The mean daily dose of Diovan in Val-HeFT was 254 mg. The study had two primary endpoints: all cause mortality (time to death) and composite mortality and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalisation for heart failure, or administration of intravenous inotropic or vasodilator agents for four hours or more without hospitalisation.

All cause mortality was similar (p=NS) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a 27.5% (95% CI: 17 to 37%) reduction in risk for time to first heart failure hospitalisation (13.9% vs. 18.5%). Results appearing to favour placebo (composite mortality and morbidity was 21.9% in placebo vs. 25.4% in valsartan group) were observed for those patients receiving the triple combination of an ACE inhibitor, a beta blocker and valsartan.

In a subgroup of patients not receiving an ACE inhibitor (n=366), the morbidity benefits were greatest. In this subgroup all-cause mortality was significantly reduced with valsartan compared to placebo by

33% (95% CI: –6% to 58%) (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo).
In patients receiving an ACE inhibitor without a beta-blocker, all cause mortality was similar (p=NS) in the valsartan (21.8%) and placebo (22.5%) groups. Composite mortality and morbidity risk was significantly reduced by 18.3% (95% CI: 8% to 28%) with valsartan compared with placebo (31.0% vs. 36.3%).
In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, oedema and rales compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

Hypertension
Administration of Diovan 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 antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.
Abrupt withdrawal of Diovan 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 randomized 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.

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Abrupt withdrawal of Diovan has not been associated with rebound hypertension or other adverse clinical events.
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5.2 Pharmacokinetic properties

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.

Excretion:
Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in 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.

In Heart failure patients:
The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

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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.

Impaired renal function
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Diovan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.
In rats, maternally toxic doses (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/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).
In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).
In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

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

[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 and associated names (see Annex I) 40 mg film-coated tablets
Valsartan
Diovan and associated names (see Annex I) 40 mg capsules, hard
Valsartan
Diovan and associated names (see Annex I) 80 mg film-coated tablets
Valsartan
Diovan and associated names (see Annex I) 80 mg capsules, hard
Valsartan
Diovan and associated names (see Annex I) 160 mg film-coated tablets
Valsartan
Diovan and associated names (see Annex I) 160 mg capsules, hard
Valsartan
Diovan and associated names (see Annex I) 320 mg film-coated tablets
Valsartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg valsartan.
Each capsule contains 40 mg valsartan.
Each film-coated tablet contains 80 mg valsartan.
Each capsule contains 80 mg valsartan.
Each film-coated tablet contains 160 mg valsartan.
Each capsule contains 160 mg valsartan.
Each film-coated tablet contains 320 mg valsartan.

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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Diovan and associated names (see Annex I) 40 mg film-coated tablets
Valsartan
Diovan and associated names (see Annex I) 40 mg capsules, hard
Valsartan
Diovan and associated names (see Annex I) 80 mg film-coated tablets
Valsartan
Diovan and associated names (see Annex I) 80 mg capsules, hard
Valsartan
Diovan and associated names (see Annex I) 160 mg film-coated tablets
Valsartan
Diovan and associated names (see Annex I) 160 mg capsules, hard
Valsartan
Diovan and associated names (see Annex I) 320 mg film-coated tablets
Valsartan
[See Annex I - To be completed nationally]

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 and associated names (see Annex I) 40 mg film-coated tablets
Diovan and associated names (see Annex I) 40 mg capsules, hard
Diovan and associated names (see Annex I) 80 mg film-coated tablets
Diovan and associated names (see Annex I) 80 mg capsules, hard
Diovan and associated names (see Annex I) 160 mg film-coated tablets
Diovan and associated names (see Annex I) 160 mg capsules, hard
Diovan and associated names (see Annex I) 320 mg film-coated tablets

[See Annex I -To be completed nationally]
Valsartan

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 IS AND WHAT IT IS USED FOR

Diovan belongs to a class of medicines known as angiotensin II receptor antagonist, 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. Diovan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

Diovan 40 mg film-coated tablets **can be used for two different conditions:**
- **to treat people after a recent heart attack** (myocardial infarction)**.** "Recent" here means between 12 hours and 10 days.
- **to treat symptomatic heart failure.** Diovan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used.
  Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Diovan 40 mg capsules, hard **can be used for two different conditions:**
- **to treat people after a recent heart attack** (myocardial infarction)**.** "Recent" here means between 12 hours and 10 days.
- **to treat symptomatic heart failure.** Diovan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure)

cannot be used.
Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Diovan 80 mg film-coated tablets **can be used for three different conditions:**

- **to treat high blood pressure.** High blood pressure increases the workload on 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.
- **to treat people after a recent heart attack** (myocardial infarction)**.** "Recent" here means between 12 hours and 10 days.
- **to treat symptomatic heart failure.** Diovan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used.
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- **to treat symptomatic heart failure.** Diovan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used.
  Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Diovan 160 mg film-coated tablets **can be used for three different conditions:**

- **to treat high blood pressure.** High blood pressure increases the workload on 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.
- **to treat people after a recent heart attack** (myocardial infarction)**.** "Recent" here means between 12 hours and 10 days.
- **to treat symptomatic heart failure.** Diovan is used when a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors (a medication to treat heart failure) cannot be used or it may be used in addition to ACE inhibitors when beta blockers (another medication to treat heart failure) cannot be used.
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  Heart failure symptoms include shortness of breath, and swelling of the feet and legs due to fluid build-up. It is caused when the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body.

Diovan 320 mg film-coated tablets **can be used**

- **to treat high blood pressure.** High blood pressure increases the workload on 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

Do not take Diovan:

- if you are **allergic** (hypersensitive) to valsartan or any of the other ingredients of Diovan .
- if you have **severe liver disease.**
- if you are **more than 3 months pregnant** (it is also better to avoid Diovan in early pregnancy - see pregnancy section).

If any of these apply to you, do not take Diovan

Take special care with Diovan:

- if you have liver disease.
- if you have severe kidney disease or if you are undergoing dialysis**.**
- if you are suffering from a narrowing of the kidney artery.
- if you have recently undergone kidney transplantation (received a new kidney).
- if you are treated after a heart attack or for heart failure, your doctor may check your kidney function.
- if you have severe heart disease other than heart failure or heart attack.
- if you are taking medicines that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin. It may be necessary to check the amount of potassium in your blood at regular intervals.
- if you suffer from aldosteronism. 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 is not recommended.
- if you have lost a lot of fluid (dehydration) caused by diarrhoea, vomiting, or high doses of water pills (diuretics).
- the use of Diovan in children and adolescents is not recommended (below the age of 18 years).
- you must tell your doctor if you think you are (or might become) pregnant. Diovan 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).

If any of these apply to you, tell your doctor before you take Diovan.

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 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 applies to both prescription and non-prescription medicines, especially:

- **other medicines that lower blood pressure**, especially **water pills** (diuretics).
- **medicines that increase the amount of potassium** in your blood. These include potassium supplements or salt substitutes containing potassium, potassium-sparing medicines and heparin.
- **certain type of pain killers** called non-steroidal anti-inflammatory medicines **(NSAIDs)**.
- **lithium**, a medicine used to treat some types of psychiatric illness.

In addition:

- if you are being **treated after a heart attack,** a combination with **ACE inhibitors** (a medication to treat heart attack) is not recommended.
- if you are being **treated for heart failure,** a triple combination with **ACE inhibitors and beta blockers** (medications to treat heart failure) is not recommended**.**

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Taking Diovan with food and drink
You can take Diovan with or without food.

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 before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Diovan. Diovan 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 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 affects you. Like many other medicines used to treat high blood pressure, Diovan may in rare cases cause dizziness and affect the ability to concentrate.

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

3. HOW TO TAKE DIOVAN

Always take Diovan exactly as your doctor has told you in order to get the best results and reduce 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 the doctor even if you are feeling well.

After a recent heart attack: After a heart attack the treatment is generally started as early as after 12 hours, usually at a low dose of 20 mg twice daily. You obtain the 20 mg dose by dividing the 40 mg tablet. Your doctor will increase this dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you as an individual patient can tolerate.
Diovan can be given together with other treatment for heart attack, and your doctor will decide which treatment is suitable for you.

Heart failure: Treatment starts generally with 40 mg twice daily. Your doctor will increase the dose gradually over several weeks to a maximum of 160 mg twice daily. The final dose depends on what you as an individual patient can tolerate.
Diovan can be given together with other treatment for heart failure, and your doctor will decide which treatment is suitable for you.

High blood pressure: The usual dose is 80 mg daily. In some cases your doctor may prescribe higher doses (e.g. 160 mg or 320 mg). He may also combine Diovan with an additional medicine (e.g. a diuretic).

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You can take Diovan with or without food. Swallow Diovan with a glass of water.
Take Diovan at about the same time each day.

If you take more Diovan 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
Do not take a double dose to make up for a forgotten dose.

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.

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

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diovan 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 symptoms need immediate medical attention:
You may experience symptoms of angioedema, such as
- swollen face, tongue or throat
- difficulty in swallowing
- hives and difficulties in breathing

If you get any of these, see a doctor immediately.

Other side effects include:

Common:
- dizziness, postural dizziness
- low blood pressure with symptoms such as dizziness
- decreased kidney function (signs of renal impairment)

Uncommon*:*
- allergic reaction with symptoms such as rash, itching, dizziness, swelling of face or lips or tongue or throat, difficulty breathing or swallowing (signs of angioedema)
- sudden loss of consciousness
- spinning sensation
- severely decreased kidney function (signs of acute renal failure)
- muscle spasms, abnormal heart rhythm (signs of hyperkalaemia)
- breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of cardiac failure)
- headache
- cough
- abdominal pain
- nausea
- diarrhea
- tiredness
- weakness

Not known:
- rash, itching, together with some of the following signs or symptoms: fever, joint pain, muscle pain, swollen lymph nodes and/or flu-like symptoms (signs of serum sickness)
- purplished-red spots, fever, itching (signs of inflammation of blood vessels also called vasculitis)
- unusual bleeding or bruising (signs of thrombocytopenia)
- muscle pain (myalgia)
- fever, sore throat or mouth ulcers due to infections (symptoms of low level of white blood cells also called neutropenia)

- decrease of level of haemoglobin and decrease of the percentage of red blood cells in the blood (which can, in severe cases, lead to anaemia)
- increase of level of potassium in the blood (which can, in severe cases, trigger muscle spasms, abnormal heart rhythm)
- elevation of liver function values (which can indicate liver damage) including an increase of bilirubin in the blood (which can, in severe cases, trigger yellow skin and eyes)
- increase of level of blood urea nitrogen and increase of level of serum creatinine (which can indicate abnormal kidney function)

The frequency of some side effects may vary depending on your condition. For example, side effects such as dizziness, and decreased kidney function, were seen less frequently in patients treated with high blood pressure than in patients treated for heart failure or after a recent heart attack.

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

- [Storage conditions statements - To be completed nationally]
- Keep out of the reach and sight of children.
- Do not use Diovan after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.
- Do not use Diovan if you notice that the pack 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 contains

[To be completed nationally]

What Diovan looks like and contents of the pack

[To be completed nationally]

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last approved in

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

[To be completed nationally]