ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, 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 1235 Wien, Austria	Lescol 20 mg - Kapseln	20 mg	Capsule, hard	Oral use
Austria	Novartis Pharma GmbH, Brunner Strasse 59 1235 Wien, Austria	Lescol 40 mg - Kapseln	40 mg	Capsule, hard	Oral use
Austria	Novartis Pharma GmbH, Brunner Strasse 59 1235 Wien, Austria	Fluvastatin "Novartis" 20 mg-Kapseln	20 mg	Capsule, hard	Oral use
Austria	Novartis Pharma GmbH, Brunner Strasse 59 1235 Wien, Austria	Fluvastatin "Novartis" 40 mg-Kapseln	40 mg	Capsule, hard	Oral use
Austria	Novartis Pharma GmbH, Brunner Strasse 59 1235 Wien, Austria	Lescol MR 80 mg – Filmtabletten	80 mg	Film-coated tablet	Oral use
Austria	Novartis Pharma GmbH, Brunner Strasse 59 1235 Wien, Austria	Fluvastatin "Novartis" MR 80 mg – Filmtabletten	80 mg	Film-coated tablet	Oral use
Belgium	Novartis Pharma N.V. Medialaan, 40 bus 1, 1800 Vilvoorde, Belgium	Lescol 20 mg, hard capsules	20 mg	Capsule, hard	Oral use
Belgium	Novartis Pharma N.V. Medialaan, 40 bus 1, 1800 Vilvoorde, Belgium	Lescol 40, hard capsules	40 mg	Capsule, hard	Oral use
Belgium	Novartis Pharma N.V. Medialaan, 40 bus 1, 1800 Vilvoorde, Belgium	Lescol Exel 80 mg prolonged-release tablet	80 mg	Prolonged-release tablet	Oral use

Bulgaria	Novartis Pharma GmbH Roonstrasse 25, 90429 Nuremberg, Germany	Lescol caps. 40 mg	40 mg	Capsule, hard	Oral use
Bulgaria	Novartis Pharma GmbH Roonstrasse 25, 90429 Nuremberg, Germany	Lescol XL prolonged release tablet 80 mg	80 mg	Prolonged-release tablet	Oral use
Cyprus	Demetriades & Papaellinas Ltd., Kasou 21, 1086 Nicosia, Cyprus	Lescol Capsule, 20mg	20 mg	Capsule, hard	Oral use
Cyprus	Demetriades & Papaellinas Ltd., Kasou 21, 1086 Nicosia, Cyprus	Lescol Capsule, 40mg	40 mg	Capsule, hard	Oral use
Cyprus	Demetriades & Papaellinas Ltd., Kasou 21, 1086 Nicosia, Cyprus	Lescol XL Prolonged release tablet 80mg	80 mg	Film-coated tablet	Oral use
Czech Republic	Novartis, s.r.o. Na Pankráci 1724/129 140 00 Praha 4 - Nusle, Czech Republic	Lescol 20 mg	20 mg	Capsule, hard	Oral use
Czech Republic	Novartis, s.r.o. Na Pankráci 1724/129 140 00 Praha 4 - Nusle, Czech Republic	Lescol 40 mg	40 mg	Capsule, hard	Oral use
Czech Republic	Novartis, s.r.o. Na Pankráci 1724/129 140 00 Praha 4 - Nusle, Czech Republic	Lescol XL	80 mg	Film-coated tablet	Oral use

Denmark	Novartis Healthcare A/S Lyngbyvej 172, 2100 København Ø, Denmark	Lescol	20 mg	Capsule, hard	Oral use
Denmark	Novartis Healthcare A/S Lyngbyvej 172, 2100 København Ø, Denmark	Lescol	40 mg	Capsule, hard	Oral use
Denmark	Novartis Healthcare A/S Lyngbyvej 172 2100 Kopenhagen Ø, Denmark	Lescol Depot	80 mg	Prolonged-release tablet	Oral use
Estonia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo Finland	Lescol 40 mg	40 mg	Capsule	Oral use
Estonia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo Finland	Lescol XL	80 mg	Prolonged-release tablet	Oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo Finland	Lescol 20 mg	20 mg	Capsule, hard	Oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo Finland	Lescol 40 mg	40 mg	Capsule, hard	Oral use
Finland	Novartis Finland Oy Metsänneidonkuja 10 FI-02130 Espoo Finland	Lescol Depot 80 mg	80 mg	Prolonged-release tablet	Oral use

France	Novartis Pharma S.A.S. 2 & 4, rue Lionel Terray, 92500 Rueil Malmaison Cédex, France	LESCOL 20 mg	20 mg	Capsule, hard	Oral use
France	Novartis Pharma S.A.S. 2 & 4, rue Lionel Terray, 92500 Rueil Malmaison Cédex, France	LESCOL 40 mg	40 mg	Capsule, hard	Oral use
France	Pierre FABRE MEDICAMENT 45, place Abel Gance 92100 Boulogne, France	Fractal 20 mg	20 mg	Capsule, hard	Oral use
France	Pierre FABRE MEDICAMENT 45, place Abel Gance 92100 Boulogne, France	Fractal 40 mg	40 mg	Capsule, hard	Oral use
France	Novartis Pharma S.A.S. 2 & 4, rue Lionel Terray, 92500 Rueil Malmaison Cédex, France	Lescol LP 80 mg	80 mg	Film-coated, modified-release tablet	Oral use
France	Pierre FABRE MEDICAMENT 45, place Abel Gance 92100 Boulogne France	Fractal LP 80 mg	80 mg	Film-coated, modified-release tablet	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg, Germany	Locol 20 mg Hartkapsel	20 mg	Capsules, hard	Oral use

Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg, Germany	Locol 40 mg Hartkapsel	40 mg	Capsules, hard	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg, Germany	Cranoc 20 mg Hartkapsel	20 mg	Capsules, hard	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg, Germany	Cranoc 40 mg Hartkapsel	40 mg	Capsules, hard	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg, Germany	Locol 80 mg Retardtabletten	80 mg	Prolonged-release tablet	Oral use
Germany	Novartis Pharma GmbH Roonstrasse 25 90429 Nürnberg, Germany	Cranoc 80mg Retardtabletten	80 mg	Prolonged-release tablet	Oral use
Germany	Grünwalder Gesundheitsproducte GmbH Ruhlandstrasse 5, 83646 Bad Töltz, Germany	Fluvastatin-Novartis 80 mg	80 mg	Prolonged-release tablet	Oral use
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km),Metamorphosis GR-144 51 Athens Greece	Lescol® Capsule, hard 20mg	20 mg	Capsule, hard	Oral use

Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km)Metamorphosis GR-144 51 Athens, Greece	Lescol® Capsule, hard 40mg	40 mg	Capsule, hard	Oral use
Greece	Novartis (Hellas) S.A.C.I. National Road No. 1 (12th Km) Metamorphosis GR-144 51 Athens, Greece	Lescol®XL Prolonged-release tablet 80mg	80 mg	Prolonged release tablet	Oral use
Hungary	Novartis Hungária Kft. Pharma Bartók Béla út 43-47, 5th Floor, 1114 Budapest, Hungary	Lescol 40 mg hard caps	40 mg	Capsule, hard	Oral use
Hungary	Novartis Hungária Kft. Pharma Bartók Béla út 43-47, 5th Floor, 1114 Budapest, Hungary	Lescol XL 80 mg retard tablet	80 mg	Prolonged-release tablet	Oral use
Iceland	Novartis Healthcare A/S Lyngbyvej 172, 2100 København Ø, Denmark	Lescol 20 mg hard caps	20 mg	Capsule, hard	Oral use
Iceland	Novartis Healthcare A/S Lyngbyvej 172, 2100 København Ø, Denmark	Lescol 40 mg hard caps	40 mg	Capsule, hard	Oral use
Iceland	Novartis Healthcare A/S Lyngbyvej 172, 2100 København Ø, Denmark	Lescol Depot 80 mg	80 mg	Prolonged-release tablet	Oral use

Ireland	Novartis Pharmaceuticals UK Limited Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom	Lescol 20mg Capsules	20 mg	Capsule, hard	Oral use
Ireland	Novartis Pharmaceuticals UK Limited Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom	Lescol 40mg Capsules	40 mg	Capsule, hard	Oral use
Ireland	Novartis Pharmaceuticals UK Limited Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom	Lescol XL 80mg prolonged release tablets	80 mg	Prolonged release tablet	Oral use
Italy	Novartis Farma S.p.A. Largo Boccioni, 1, 21040 Origgio (VA), Italy	Lescol	20 mg	Capsule, hard	Oral use
Italy	Novartis Farma S.p.A. Largo Boccioni, 1, 21040 Origgio (VA), Italy	Lescol	40 mg	Capsule, hard	Oral use
Italy	ITALFARMACO S.p.A. Viale Fulvio Testi, 330 20126 Milano Italy	Lipaxan	20 mg	Capsule, hard	Oral use
Italy	ITALFARMACO S.p.A. Viale Fulvio Testi, 330 20126 Milano Italy	Lipaxan	40 mg	Capsule, hard	Oral use

Italy	UCB PHARMA S.p.A Via Gadames, 57 20151 Milano Italy	Primesin	20 mg	Capsule, hard	Oral use
Italy	UCB PHARMA S.p.A Via Gadames, 57 20151 Milano Italy	Primesin	40 mg	Capsule, hard	Oral use
Italy	SANDOZ S.p.A Address: Largo Umberto Boccioni 1 I-21040 Origgio / VA Italy	FLUVASTATINA Sandoz	20 mg	Capsule, hard	Oral use
Italy	SANDOZ S.p.A Address: Largo Umberto Boccioni 1 I-21040 Origgio / VA Italy	FLUVASTATINA Sandoz 40 mg hard capsules	40 mg	Capsule, hard	Oral use
Italy	Novartis Farma S.p.A. Largo Boccioni, 1, 21040 Origgio (VA), Italy	Lescol 80 mg	80 mg	Prolonged-release tablet	Oral use
Italy	ITALFARMACO S.p.A. Viale Fulvio Testi, 330 20126 Milano Italy	Lipaxan 80 mg	80 mg	Prolonged-release tablet	Oral use
Italy	UCB PHARMA S.p.A Via Gadames, 57 20151 Milano Italy	Primesin 80 mg	80 mg	Prolonged-release tablet	Oral use
Latvia	Novartis Finland OY Metsänneidonkuja 10 FIN-02130 Espoo Finland	Lescol XL 80 mg	80 mg	Prolonged-release tablet	Oral use

Lithuania	Novartis Finland Oy Metsänneidonkuja 10 FIN-02130 Espoo, Finland	Lescol XL	80 mg	Prolonged-release tablet	Oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg, Germany	Locol 20 mg hard caps	20 mg	Capsules, hard	Oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg, Germany	Locol 40 mg hard caps	40 mg	Capsules, hard	Oral use
Luxembourg	Novartis Pharma GmbH Roonstrasse 25 D-90429 Nürnberg, Germany	Locol 80 mg Retard tablet	80 mg	Prolonged-release tablet	Oral use
Malta	Novartis Pharmaceuticals UK Limited Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom	Lescol	20 mg	Capsule, hard	Oral use
Malta	Novartis Pharmaceuticals UK Limited Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom	Lescol	40 mg	Capsule, hard	Oral use
Malta	Novartis Pharmaceuticals UK Limited Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom	Lescol XL	80 mg	Film-coated tablet	Oral use

Norway	Novartis Norge AS, Postboks 237 Økern, 0510 Oslo, Norway	LESCOL	20 mg	Capsule, hard	Oral use
Norway	Novartis Norge AS, Postboks 237 Økern, 0510 Oslo, Norway	LESCOL	40 mg	Capsule, hard	Oral use
Norway	Novartis Norge AS, Postboks 237 Økern, 0510 Oslo, Norway	LESCOL DEPOT 80 mg	80 mg	Prolonged-release tablet	Oral use
Netherlands	Novartis Pharma B.V. P.O. Box 241 6800 LZ Arnhem The Netherlands	Lescol 20 mg, capsules	20 mg	Capsule, hard	Oral use
Netherlands	Novartis Pharma B.V. Raapopseweg 1 ,6824 DP Arnhem, The Netherlands	Lescol 40 mg, capsules	40 mg	Capsule, hard	Oral use
Netherlands	Novartis Pharma B.V. Raapopseweg 1 ,6824 DP Arnhem, The Netherlands	Lescol XL 80, tablet	80 mg	Film-coated tablet	Oral use
Poland	Novartis Pharma GmbH Roonstrasse 25, D- 90429 Nürnberg, Germany	Lescol	20 mg	Capsule, hard	Oral use
Poland	Novartis Pharma GmbH Roonstrasse 25, D-90429 Nürnberg, Germany	Lescol	40 mg	Capsule, hard	Oral use
Poland	Novartis Pharma GmbH Roonstrasse 25, D-90429 Nürnberg, Germany	Lescol XL	80 mg	Prolonged-release tablet	Oral use

Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edif. 8 , Quinta de Beloura 2710-444, Sintra, Portugal	Lescol	20 mg	Capsule, hard	Oral use
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edif. 8 , Quinta de Beloura 2710-444, Sintra, Portugal	Lescol	40 mg	Capsule, hard	Oral use
Portugal	Bialport – Produtos Farmacêuticos, S.A. À Av. da Siderurgia Nacional – 4745-457 S. Mamede do Coronado Portugal	Cardiol 20	20 mg	Capsule, hard	Oral use
Portugal	Bialport – Produtos Farmacêuticos, S.A. À Av. da Siderurgia Nacional – 4745-457 S. Mamede do Coronado Portugal	Cardiol 40	40 mg	Capsule, hard	Oral use
Portugal	Laboratório Normal - Produtos Farmacêuticos, S.A. Rua do Centro empresarial, Edifício 8, Quinta da Beloura 2710-444 Sintra Portugal	Canef	20 mg	Capsule, hard	Oral use

Portugal	Laboratório Normal - Produtos Farmacêuticos, S.A. Rua do Centro empresarial, Edifício 8, Quinta da Beloura 2710-444 Sintra Portugal	Canef	40 mg	Capsule, hard	Oral use
Portugal	Novartis Farma - Produtos Farmacêuticos S.A. Rua do Centro Empresarial, Edif. 8 , Quinta de Beloura 2710-444, Sintra, Portugal	Lescol XL	80 mg	Prolonged-release tablet	Oral use
Portugal	Bialport – Produtos Farmacêuticos, S.A. À Av. da Siderurgia Nacional – 4745-457 S. Mamede do Coronado Portugal	Cardiol XL	80 mg	Prolonged-release tablet	Oral use
Portugal	Laboratório Normal - Produtos Farmacêuticos, S.A. Rua do Centro empresarial, Edifício 8, Quinta da Beloura 2710-444 Sintra Portugal	Canef 80 mg	80 mg	Prolonged-release tablet	Oral use
Romania	NOVARTIS PHARMA GmbH Roonstrasse 25, D-90429 Nürnberg, Germany	LESCOL 20 mg	20 mg	Capsule, hard	Oral use
Romania	NOVARTIS PHARMA GmbH Roonstrasse 25, D-90429 Nürnberg, Germany	LESCOL 40 mg	40 mg	Capsule, hard	Oral use

Romania	NOVARTIS PHARMA GmbH Roonstrasse 25, D-90429 Nürnberg, Germany	LESCOL XL	80 mg	Prolonged-release tablet	Oral use
Slovak Republic	Novartis, s.r.o. U Nákladového nádraží 10, 13000 Prague 3, Czech Republic	Lescol 20 mg	20 mg	Capsule, hard	Oral use
Slovak Republic	Novartis, s.r.o. U Nákladového nádraží 10, 13000 Prague 3, Czech Republic	Lescol 40 mg	40 mg	Capsule, hard	Oral use
Slovak Republic	Novartis, s.r.o. U Nákladového nádraží 10, 13000 Prague 3, Czech Republic	Lescol XL 80 mg	80 mg	Prolonged-release tablet	Oral use
Slovenia	Novartis Pharma GmbH Roonstrasse 25, D-90429 Nürnberg, Germany	Lescol 40 mg trde kapsule	40 mg	Capsule, hard	Oral use
Slovenia	Novartis Pharma GmbH Roonstrasse 25, D-90429 Nürnberg, Germany	Lescol XL 80 mg tablete s podaljšanim sproščanjem	80 mg	Prolonged-release tablet	Oral use
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanas, N° 764, 08013, Barcelona, Spain	Lescol 20 mg caps	20 mg	Capsule, hard	Oral use

Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanas, N° 764, 08013, Barcelona, Spain	Lescol 40 mg caps	40 mg	Capsule, hard	Oral use
Spain	Novartis Farmacéutica, S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona, Spain	Liposit 20 mg caps	20 mg	Capsule, hard	Oral use
Spain	Novartis Farmacéutica, S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona, Spain	Liposit 40 mg caps	40 mg	Capsule, hard	Oral use
Spain	Novartis Farmacéutica, S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona, Spain	Vaditon 20 mg caps	20 mg	Capsule, hard	Oral use
Spain	Novartis Farmacéutica, S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona, Spain	Vaditon 40 mg caps	40 mg	Capsule, hard	Oral use
Spain	Novartis Farmacéutica,S.A. Av. Diagonal, 507 08029 Barcelona, Spain	Digaril 20 mg caps	20 mg	Capsule, hard	Oral use
Spain	Novartis Farmacéutica, S.A. Av. Diagonal, 507 08029 Barcelona, Spain	Digaril 40 mg caps	40 mg	Capsule, hard	Oral use

Spain	GRÜNENTHAL PHARMA, S.A. Doctor Zamenhof nº 36 28027 Madrid, Spain	Lymetel 20 mg caps	20 mg	Capsule, hard	Oral use
Spain	GRÜNENTHAL PHARMA, S.A. Doctor Zamenhof nº 36 28027 Madrid, Spain	Lymetel 40 mg caps	40 mg	Capsule, hard	Oral use
Spain	Novartis Farmacéutica S.A. Gran Via de les Corts Catalanas, N° 764, 08013, Barcelona, Spain	Lescol prolib 80 mg	80 mg	Prolonged-release tablet	Oral use
Spain	Novartis Farmacéutica, S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona Spain	Liposit Prolib 80	80 mg	Prolonged-release tablet	Oral use
Spain	Novartis Farmacéutica, S.A. Gran Via de les Corts Catalanes, 764 08013 Barcelona Spain	Vaditon Prolib 80 mg	80 mg	Prolonged-release tablet	Oral use
Spain	Novartis Farmacéutica, S.A. Av. Diagonal, 507 08029 Barcelona Spain	Digaril Prolib 80 mg	80 mg	Prolonged-release tablet	Oral use

Spain	Laboratorios Andrómaco, S.A. Doctor Zamenhof nº 36 28027 Madrid Spain	Lymetel Prolib 80 mg	80 mg	Prolonged-release tablet	Oral use
Sweden	Novartis Sverige AB Box 1150, 18311 Täby, Sweden	Lescol	20 mg	Capsule, hard	Oral use
Sweden	Novartis Sverige AB Box 1150, 18311 Täby, Sweden	Lescol	40 mg	Capsule, hard	Oral use
Sweden	Novartis Sverige AB Box 1150, 18311 Täby, Sweden	Lescol Depot	80 mg	Prolonged-release tablet	Oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd (Trading as Sandoz Pharmaceuticals) Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	LESCOL CAPSULES 20MG	20 mg	Capsule, hard	Oral use
United Kingdom	Novartis Pharmaceuticals UK Ltd (Trading as Sandoz Pharmaceuticals) Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	LESCOL CAPSULES 40MG	40 mg	Capsule, hard	Oral use

United Kingdom	Novartis Pharmaceuticals UK Ltd (Trading as Sandoz Pharmaceuticals) Frimley Business Park Frimley, Camberley Surrey GU16 7SR United Kingdom	LESCOLXL 80 mg Prolonged Release Tablets	80 mg	Prolonged-release tablet	Oral use

ANNEX II

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

SCIENTIFIC CONCLUSIONS

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

Lescol, a fully synthetic cholesterol-lowering agent, is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Lescol IR (Lescol immediate release) 20 mg and 40 mg capsules were first registered in 1993. The first marketing authorization was issued for Lescol XL (Lescol extended release) 80 mg tablets in 2000. Lescol 20 mg, 40 mg are hard gelatine capsules and Lescol 80 mg is a modified release film coated tablet.

The MAH Novartis completed the EU Work Sharing Project on paediatric wording on 24 July 2007. The Reference Member State was Germany (BfArM). Following the procedure the MAH submitted the approved paediatric wording to all EU member states.

Lescol was included in the list of products for Summary of Product Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended. The harmonisation of the quality aspects was not part of this Article 30 procedure.

Section 4.1 – Therapeutic Indications

- **Primary hypercholesterolaemia and mixed dyslipidaemia**

The CHMP agreed with the MAH that additional statements on the exclusion of certain lipoprotein disorders (e.g homozygous variants of familial hypercholesterolaemia and other Fredrickson types with predominant hypertriglyceridemia, or secondary forms of hypercholesterolaemia) are not required in the indication section. The CHMP also agreed with the MAH's proposal not to include a recommendation to assess causes of secondary hypercholesterolaemia in the indications section. The MAH's proposal to include response to diet and other measures (e.g. exercise, weight reduction) was also considered to be acceptable as it is in line with other statin product information texts.

The CHMP agreed with the following wording proposed by the MAH for this indication:

'Treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.'

Paediatric population

The open-label design and the lack of a placebo control group did not allow a solid conclusion to be drafted regarding the efficacy and safety in this population due to some methodological limitations. Furthermore, no paediatric indication was granted through the EU Paediatric Worksharing project and no new clinical data were submitted for this Art 30 procedure. Therefore the CHMP agreed that the available clinical data could not be considered as adequate information to support a paediatric indication statement.

- **Secondary prevention of major cardiac events in adults with coronary heart disease (CHD) after percutaneous coronary interventions (PCI)**

The secondary prevention indication in patients after PCI is based on the Lescol Intervention Prevention Study (LIPS). LIPS (study LES-EUR-01) was conducted to determine if fluvastatin therapy reduced the long-term risk of MACE (i.e. cardiac death, non-fatal myocardial infarction (MI) and coronary revascularisation) in CHD patients after a successful PCI. The incidence of MACE was 21.4% on fluvastatin and 26.7% on placebo. Based on the Cox regression analysis the risk ratio for MACE was estimated at 0.78, equivalent to a statistically significant 22% reduction in the risk of MACE for patients treated in the Lescol group compared to the placebo group. The risk ratios of cardiac death (RR 0.53) and cardiac death or nonfatal MI (RR 0.69) were also less than 1 but the study was not powered for these endpoints. This result was independent of baseline total cholesterol levels.

Overall Lescol was safe and well tolerated and the observed safety profile consistent with the known adverse event profile.

The CHMP agreed with the following wording proposed by the MAH for this indication:
'Secondary prevention of major adverse cardiac events in adults with coronary heart disease after percutaneous coronary interventions (see section 5.1).'

Section 4.2 - Posology and method of administration

- **Primary hypercholesterolaemia and mixed dyslipidaemia**

Starting dose recommendation
The CHMP agreed that the proposed starting dose of 40 mg in patients requiring LDL-C reductions of ≥25% is justified by the clinical data provided. From an efficacy perspective the 80 mg dose provided reliable LDL-C lowering of at least 30% vs baseline at 24 weeks. An analysis from the pooled clinical trial databases of Lescol IR or Lescol XL registration studies provided by the MAH showed that the likelihood of achieving LDL reductions of ≥25% was modest with a 20 mg daily dosage of fluvastatin. Also, the relative reduction in LDL-C is similar across different baseline levels of LDL-C. Therefore it was the recommendation of the CHMP that the starting dose of 40mg uptitrated to 80mg/day, taking into account patient response would be more appropriate from an efficacy and safety perspective. This is also in line with all other statins posology recommendations.

The CHMP agreed with the following wording for a flexible initial dosing of 40-80mg:
'The recommended dosing range is 20 to 80 mg/day. For patients requiring LDL-C reduction to a goal of < 25% a starting dose of 20 mg may be used as one capsule in the evening. For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule in the evening. The dose may be uptitrated to 80 mg daily, administered as a single dose (one Lescol XL tablet) at any time of the day or as one 40 mg capsule given twice daily (one in the morning and one in the evening).'

Concomitant treatment with other lipid modifying drugs
The MAH submitted published data to support the efficacy and safety of Lescol/Lescol XL in combination with nicotinic acid, cholestyramine, or fibrates. However, since an increased risk of myopathy has been observed in patients receiving other HMG-CoA reductase inhibitors together with fibrates or niacin, these combinations should be used with caution.

The following wording proposed by the MAH was considered to be acceptable for the CHMP:
'Lescol is efficacious in monotherapy. When Lescol is used in combination with cholestyramine or other resins, it should be administered at least 4 hours after the resin to avoid significant interaction due to binding of the drug to the resin. In cases where coadministration with a fibrate or niacin is necessary, the benefit and the risk of concurrent treatment should be carefully considered (for use with fibrates or niacin see section 4.5).'

- **Secondary prevention of major cardiac events in adults with coronary heart disease (CHD) after percutaneous coronary interventions (PCI)**

For the secondary CHD prevention indication in patients after transcatheter therapy/PCI, a dose of 80 mg was generally proposed as adequate. In the LIPS study which was the basis for this indication, the 80 mg daily dose of fluvastatin (i.e., Lescol IR 40 mg BID) was used as starting dose.

The CHMP agreed with the following wording proposed by the MAH:
'In patients with coronary heart disease after percutaneous coronary interventions the appropriate daily dose is 80 mg.'

Time of medication intake and meals
The recommendation that Lescol capsules can be taken regardless of meals is largely consistent across the EU Member States.

Dose titration intervals
The data on LDL-C lowering at different time points based on the pooled efficacy analysis from the Lescol XL registration program supports the following recommendation:

'The maximum lipid-lowering effect with a given dose is achieved within 4 weeks. Dose adjustments should be made at intervals of 4 weeks or more.'

Special populations
Children and adolescents
Minor modifications from the Worksharing Project wording reflect the paediatric data and were considered to be acceptable.
The CHMP agreed with the following wording:
'Children and adolescents with heterozygous familial hypercholesterolaemia
'Prior to initiating treatment with Lescol/Lescol XL in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia, the patient should be placed on a standard cholesterol-lowering diet, and continued during treatment.

The recommended starting dose is one 20 mg Lescol capsule. Dose adjustments should be made at 6-week intervals. Doses should be individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum daily dose administered is 80 mg either as Lescol capsules 40 mg twice daily or as one Lescol 80 mg tablet once daily.

The use of fluvastatin in combination with nicotinic acid, cholestyramine, or fibrates in children and adolescents has not been investigated.

Lescol/Lescol XL has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia.'

Elderly patients
The dosage recommendations in elderly patients are consistent across the Member States in stating that no dose adjustments are required.

Impaired liver function
A statement that Lescol/Lescol XL is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases is included in this section 4.2 as well as in sections 4.3, 4.4 and 5.2.

Impaired kidney function
The analyses from the Lescol pooled clinical trial database and the ALERT study presented by the MAH has provided further data regarding the efficacy and safety of fluvastatin 40-80mg in patients with renal impairment. However it is still not possible to draw appropriate conclusions regarding the positive benefit-risk of doses >40mg in severe renal impairment, since a direct dose-level comparison between Lescol 40 vs 80mg/day was not possible, and the study population of patients with severe renal impairment was limited. Nevertheless, the available data suggest that no serious safety concern is present for Lescol as compared to placebo, for all renal function categories. There is no obvious reason therefore, to contraindicate doses>40mg in severe renal impairment, but it would be more appropriate to initiate these high doses with caution.

Based on the recommendation given by the CHMP, the following wording proposed was agreed:
'Renal Impairment
Lescol/Lescol XL is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency. No dose adjustments are therefore necessary in these patients however, due to limited

experience with doses >40mg/day in case of severe renal impairment (CrCL <0,5 mL/sec or 30 mL/min), these doses should be initiated with caution.'

Section 4.3 - Contra-indications
There is consistency across all EU Member States in contraindicating Lescol/Lescol XL for patients with known hypersensitivity to fluvastatin or any of the excipients and in patients with active liver disease, or unexplained, persistent elevations in serum transaminases. Considering the possibility of teratogenicity with statins as a class, the benefit risk for the use in pregnancy has been considered as negative for statins including fluvastatin and the contraindication in pregnancy justified.

Section 4.4 - Special warnings and precautions for use
The CHMP considered it reasonable to maintain the recommendations on liver function testing which have been implemented in clinical practice over the last decade(s), although routine monitoring of transaminases has been discouraged more recently by various experts.

The text proposed regarding recommendations regarding skeletal muscle reflects the wording that is currently implemented in the majority of EU Member States and is in line with various published recommendations on warnings and precautions on skeletal muscle. The statement that isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with ciclosporin and the statement related to concomitant administration of fluvastatin and colchicines has been included in the MAH's proposal and agreed by the CHMP. The particular reference to heart transplant conditions and ciclosporin seems sufficiently covered by the general statement for immunosuppressive drugs.

Based on the Pharmacovigilance Working Party (PhVWP) Report on the association of HMG CoA reductase inhibitors, this section has also been updated to include interstitial lung disease. The CHMP agreed with the wording proposed for the paediatric population in line with the wording agreed during the EU Worksharing Project.

No clinical data is available for Lescol in patients with homozygous familial hypercholesterolaemia (HoFH) and is stated in this section.

Section 4.5 - Interaction with other medicinal products and other forms of interaction
Food interactions were restricted to grapefruit juice only.

Section 4.6 - Pregnancy and lactation
The MAH agreed that the contraindication is medically justified as a harm to the fetus (or to the breastfed newborn) with statins cannot be excluded. The recommendations that women of childbearing potential have to use effective contraception and that treatment should be discontinued from women who become pregnant while taking Lescol/Lescol XL, has been included.

In the vast majority of EU Member States Lescol/Lescol XL is contraindicated in breastfeeding women and statement to this effect has been included by the MAH.

Section 4.7 - Effects on ability to drive and use machines
A statement that no studies on the effects on the ability to drive and use machines have been performed has been included.

Section 4.8 - Undesirable effects
The undesirable effects currently listed are consistently represented in the SPCs of the EU Member States, except for anaphylactic reaction, which was recently included. The Product Information (PI) has also been updated according to the CHMP PhVWP Report on HMG CoA reductase inhibitors to include the following adverse events that have been reported with some statins: sleep disturbances, including insomnia and nightmares, memory loss, sexual dysfunction, depression, exceptional cases of interstitial lung disease,

especially with long term therapy. The MAH has also implemented the statement from the EU worksharing Project.

Section 4.9 – Overdose
An overall recommendation to monitor liver function and CK levels seemed a reasonable approach considering that effects on liver and muscle may be generally expected in statin overdosage. The broad recommendation of "supportive measures" would cover gastrointestinal decontamination measures, if appropriate.

Section 5.1 - Pharmacodynamic properties
Due to the heterogeneity in the presentation of the clinical trial data for dyslipidaemia across the various Member States, a concise approach including data on Lescol IR from the pooled placebo-controlled studies and data from the Lescol XL development program has been proposed. Results at 24-week from both programs have been presented in a single table with limited repetition in the text, in order to improve clarity of information and ease of use.

A summary of the clinical trial data from the Lipoprotein and Coronary Atherosclerosis Study (LCAS) has been proposed by the MAH, including a statement that the significance of angiographic findings was not known.

A summary of the clinical trial data from the Lescol Intervention Prevention Study (LIPS) that is currently implemented in the largest number of Member States appeared most concise and was therefore proposed by the MAH. The information that the study was conducted in patients after PCI was added.

The paediatric information from the EU Worksharing Project has also been implemented with minor editorial changes.

Section 5.2 - Pharmacokinetic properties
The CHMP agreed with the wording proposed by the MAH.

Section 5.3 - Preclinical safety data
During the procedure, the MAH was requested to summarise this section, describing the results of the preclinical studies in brief and qualitative statements, according to the Guideline on the Summary of Product Characteristics. The MAH's proposal was amended and considered to be acceptable by the CHMP:

'The conventional studies, including safety pharmacology, genotoxicity, repeated dose toxicity, carcinogenicity and toxicity on reproduction studies did not indicate other risks for the patient than those expected due to the pharmacological mechanism of action. A variety of changes were identified in toxicity studies that are common to HMG-CoA reductase inhibitors. Based on clinical observations, liver function tests are already recommended (see section 4.4). Further toxicity seen in animals was either not relevant for human use or occurred at exposure levels sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Despite the theoretical considerations concerning the role of cholesterol in embryo development, animal studies did not suggest an embryotoxic and teratogenic potential of fluvastatin.'

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

Whereas

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

- the Summary of Products Characteristics, 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 Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Lescol and associated names (see Annex I).

The CHMP concluded that the following indications are supported by the available data submitted by the MAH:

- Treatment of primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

- Secondary prevention of major adverse cardiac events in adults with coronary heart disease after percutaneous coronary interventions (see section 5.1).

The CHMP was of the opinion that the data submitted by the MAH intended to support the indication *"Lescol/Lescol XL is indicated to slow the progression of coronary atherosclerosis in adults with primary hypercholesterolaemia and coronary heart disease"* was not clinically meaningful and therefore a positive benefit/risk could not be established.

The paediatric indication was not granted during the assessment of paediatric data through the EU work-sharing procedure. Since no new data was submitted during this harmonisation referral, the CHMP confirmed that a paediatric indication could not be granted during this Article 30 harmonisation referral. However appropriate wording for the paediatric population were included in the sections agreed during the EU Worksharing procedure; sections 4.2, 4.4, 4.8, 5.1 and 5.2.

Since the available data suggest that there is no serious safety concern for Lescol as compared to placebo, for all renal function categories, the CHMP agreed that doses of >40mg in severe renal impairment would not be contraindicated, but that it would be necessary to initiate these high doses with caution. Regarding section 5.3 Preclinical safety data, the MAH's proposal was amended and considered to be acceptable by the CHMP.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lescol and associated names (see Annex I) 20 mg capsules, hard
Lescol and associated names (see Annex I) 40 mg capsules, hard
Lescol XL and associated names (see Annex I) 80 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: fluvastatin (as fluvastatin sodium)

One capsule of Lescol contains 21.06 mg fluvastatin sodium equivalent to 20 mg fluvastatin free acid
or 42.12 mg fluvastatin sodium equivalent to 40 mg fluvastatin free acid.
One prolonged-release tablet of Lescol XL contains 84.24 mg fluvastatin sodium equivalent to 80 mg fluvastatin free acid.

Excipients:
[To be completed nationally]

3. PHARMACEUTICAL FORM

Capsule, hard
Capsule, hard
Prolonged-release tablet

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dyslipidaemia

Treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Secondary prevention in coronary heart disease
Secondary prevention of major adverse cardiac events in adults with coronary heart disease after percutaneous coronary interventions (see section 5.1).

4.2 Posology and method of administration

Adults
Dyslipidaemia
Prior to initiating treatment with Lescol/Lescol XL, patients should be placed on a standard cholesterol-lowering diet, which should be continued during treatment.
Starting and maintenance doses should be individualized according to the baseline LDL-C levels and the treatment goal to be accomplished.
The recommended dosing range is 20 to 80 mg/day. For patients requiring LDL-C reduction to a goal of < 25% a starting dose of 20 mg may be used as one capsule in the evening. For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule in the evening. The

dose may be uptitrated to 80 mg daily, administered as a single dose (one Lescol XL tablet) at any time of the day or as one 40 mg capsule given twice daily (one in the morning and one in the evening).

The maximum lipid-lowering effect with a given dose is achieved within 4 weeks. Dose adjustments should be made at intervals of 4 weeks or more.

Secondary prevention in coronary heart disease
In patients with coronary heart disease after percutaneous coronary interventions the appropriate daily dose is 80 mg.

Lescol is efficacious in monotherapy. When Lescol is used in combination with cholestyramine or other resins, it should be administered at least 4 hours after the resin to avoid significant interaction due to binding of the drug to the resin. In cases where coadministration with a fibrate or niacin is necessary, the benefit and the risk of concurrent treatment should be carefully considered (for use with fibrates or niacin see section 4.5).

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
Prior to initiating treatment with Lescol/Lescol XL in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia, the patient should be placed on a standard cholesterol-lowering diet, and continued during treatment.

The recommended starting dose is one 20 mg Lescol capsule. Dose adjustments should be made at 6-week intervals. Doses should be individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum daily dose administered is 80 mg either as Lescol capsules 40 mg twice daily or as one Lescol 80 mg tablet once daily.

The use of fluvastatin in combination with nicotinic acid, cholestyramine, or fibrates in children and adolescents has not been investigated.

Lescol/Lescol XL has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia.

Renal Impairment
Lescol/Lescol XL is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency. No dose adjustments are therefore necessary in these patients however, due to limited experience with doses >40mg/day in case of severe renal impairment (CrCL <0,5 mL/sec or 30 mL/min), these doses should be initiated with caution.

Hepatic Impairment
Lescol/Lescol XL is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.3, 4.4 and 5.2).

Elderly population
No dose adjustments are necessary in this population.

Method of administration
Lescol capsules and Lescol XL tablets can be taken with or without meals and should be swallowed as whole with a glass of water.

4.3 Contraindications

Lescol/Lescol XL is contraindicated:

- in patients with known hypersensitivity to fluvastatin or any of the excipients.
- in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.2, 4.4 and 4.8).
- during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Liver function

As with other lipid-lowering agents, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of treatment or elevation in dose and periodically thereafter in all patients. Should an increase in aspartate aminotransferase or alanine aminotransferase exceed 3 times the upper limit of normal and persist, therapy should be discontinued. In very rare cases, possibly drug-related hepatitis was observed that resolved upon discontinuation of treatment.

Caution should be exercised when Lescol/Lescol XL is administered to patients with a history of liver disease or heavy alcohol ingestion.

Skeletal muscle

Myopathy has rarely been reported with fluvastatin. Myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values, myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.

Creatine kinase measurement

There is no current evidence to require routine monitoring of plasma total CK or other muscle enzyme levels in asymptomatic patients on statins. If CK has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes the value interpretation difficult.

Before treatment

As with all other statins physicians should prescribe fluvastatin with caution in patients with predisposing factors for rhabdomyolysis and its complications. A creatine kinase level should be measured before starting fluvastatin treatment in the following situations:

- Renal impairment.
- Hypothyroidism.
- Personal or familial history of hereditary muscular disorders.
- Previous history of muscular toxicity with a statin or fibrate.
- Alcohol abuse.
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5x ULN), levels should be re-measured within 5 to 7 days later to confirm the results. If CK levels are still significantly elevated (> 5x ULN) at baseline, treatment should not be started.

Whilst on treatment

If muscular symptoms like pain, weakness or cramps occur in patients receiving fluvastatin, their CK levels should be measured. Treatment should be stopped if these levels are found to be significantly elevated (> 5x ULN).

If muscular symptoms are severe and cause daily discomfort, even if CK levels are elevated to ≤ 5x ULN, treatment discontinuation should be considered.

Should the symptoms resolve and CK levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive agents (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with ciclosporin and fluvastatin with colchicines. Lescol/Lescol XL should be used with caution in patients receiving such concomitant medicine (see section 4.5).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
In patients aged < 18 years, efficacy and safety have not been studied for treatment periods longer than two years. No data are available about the physical, intellectual and sexual maturation for prolonged treatment period. The long-term efficacy of Lescol/Lescol XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established. (see section 5.1).

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1). In the case of pre-pubertal children, as experience is very limited in this group, the potential risks and benefits should be carefully evaluated before the initiation of treatment.

Homozygous familial hypercholesterolaemia
No data are available for the use of fluvastatin in patients with the very rare condition of homozygous familial hypercholesterolaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Fibrates and niacin
Concomitant administration of fluvastatin with bezafibrate, gemfibrozil, ciprofibrate or niacin (nicotinic acid) has no clinically relevant effect on the bioavailability of fluvastatin or the other lipid-lowering agent. Since an increased risk of myopathy and/or rhabdomyolysis has been observed in patients receiving HMG-CoA reductase inhibitors together with any of these molecules, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

Colchicines
Myotoxicity, including muscle pain and weakness and rhabdomyolysis, has been reported in isolated cases with concomitant administration of colchicines. The benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

Ciclosporin

Studies in renal transplant patients indicate that the bioavailability of fluvastatin (up to 40 mg/day) is not elevated to a clinically significant extent in patients on stable regimens of ciclosporin. The results from another study in which Lescol XL tablets (80 mg fluvastatin) was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (C_{max}) were increased 2-fold compared to historical data in healthy subjects. Although these increases in fluvastatin levels were not clinically significant, this combination should be used with caution. Starting and maintenance dose of fluvastatin should be as low as possible when combined with ciclosporin.

Both Lescol capsules(40 mg fluvastatin) and Lescol XL tablets (80 mg fluvastatin) had no effect on the bioavailability of ciclosporin when co-administered.

Warfarin and other coumarin derivatives
In healthy volunteers, the use of fluvastatin and warfarin (single dose) did not adversely influence warfarin plasma levels and prothrombin times compared to warfarin alone.
However, isolated incidences of bleeding episodes and/or increases prothrombin times have been reported very rarely in patients on fluvastatin receiving concomitant warfarin or other coumarin derivatives. It is recommended that prothrombin times are monitored when fluvastatin treatment is initiated, discontinued, or the dosage changes in patients receiving warfarin or other coumarin derivatives.

Rifampicin
Administration of fluvastatin to healthy volunteers pre-treated with rifampicin (rifampin) resulted in a reduction of the bioavailability of fluvastatin by about 50%. Although at present there is no clinical evidence that fluvastatin efficacy in lowering lipid levels is altered, for patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis), appropriate adjustment of fluvastatin dosage may be warranted to ensure a satisfactory reduction in lipid levels.

Oral antidiabetic agents
For patients receiving oral sulfonylureas (glibenclamide (glyburide), tolbutamide) for the treatment of non-insulin-dependent (type 2) diabetes mellitus (NIDDM), addition of fluvastatin does not lead to clinically significant changes in glycaemic control. In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and $t_{½}$ of glibenclamide by approximately 50%, 69%, and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin, and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

Bile acid sequestrants
Fluvastatin should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding of the resin.

Fluconazole
Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure and peak concentration of fluvastatin by about 84% and 44%. Although there was no clinical evidence that the safety profile of fluvastatin was altered in patients pre-treated with fluconazole for 4 days, caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Histamine H2-receptor antagonists and proton pump inhibitors
Concomitant administration of fluvastatin with cimetidine, ranitidine or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance.

Phenytoin

The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin is relatively small and not clinically significant. Thus routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin.

Cardiovasular agents
No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with propranaolol, digoxin, losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

Itraconazole and erythromycin
Concomitant administration of fluvastatin with the potent cytochrome P450 (CYP) 3A4 inhibitors itraconazole and erythromycin has minimal effects on the bioavailability of fluvastatin. Given the minimal involvement of this enzyme in the metabolism of fluvastatin, it is expected that other CYP3A4 inhibitors (e.g. ketoconazole, ciclosporin) are unlikely to affect the bioavailability of fluvastatin.

Grapefruit juice
Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin is not expected to interact with grapefruit juice.

4.6 Pregnancy and lactation

Pregnancy
There is insufficient data on the use of fluvastatin during pregnancy.

Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause foetal harm when administered to pregnant women. Therefore, Lescol/Lescol XL is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception.

If a patient becomes pregnant while taking Lescol/Lescol XL, therapy should be discontinued.

Lactation
Based on preclinical data, it is expected that fluvastatin is excreted into human milk. There is insufficient information on the effects of fluvastatin in newborns / infants.

Lescol/Lescol XL is contraindicated in breastfeeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most commonly reported adverse reactions are mild gastrointestinal symptoms, insomnia and headache.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

Blood and lymphatic system disorders		
	Very rare:	Thrombocytopenia
Immune system disorders		
	Very rare:	Anaphylactic reaction
Psychiatric disorders		
	Common:	Insomnia
Nervous system disorders		
	Common:	Headache
	Very rare:	Paraesthesia, dysaesthesia, hypoaesthesia also known to be associated with the underlying hyperlipidaemic disorders
Vascular disorders		
	Very rare:	Vasculitis
Gastrointestinal disorders		
	Common:	Dyspepsia, abdominal pain, nausea
	Very rare:	Pancreatitis
Hepatobiliary disorders		
	Very rare:	Hepatitis
Skin and subcutaneous tissue disorders		
	Rare:	Hypersensitivity reactions such as rash, urticaria
	Very rare:	Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema
Musculoskeletal and connective tissue disorders		
	Rare:	Myalgia, muscle weakness, myopathy
	Very rare:	Rhabdomyolysis, myositis, lupus erythematosus-like reactions

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Paediatric population

Children and adolescents with heterozygous familial hypercholesterolaemia

The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia assessed in 114 patients aged 9 to17 years treated in two open-label non-comparative clinical trials was similar to the one observed in adults. In both clinical trials no effect was observed on growth and sexual maturation. The ability of the trials to detect any effect of treatment in this area was however low.

Laboratory findings

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Based on pooled analyses of controlled clinical trials confirmed elevations of alanine aminotransferase or aspartate aminotranferase levels to more than 3 times the upper limit of normal occurred in 0.2% on Lescol capsules 20 mg/day, 1.5% to 1.8% on Lescol capsules 40 mg/day, 1.9% on Lescol XL tablets 80 mg/day and in 2.7% to 4.9% on twice daily Lescol capsules 40 mg. The majority of patients with these abnormal biochemical findings were asymptomatic. Marked elevations of CK levels to more than 5x ULN developed in a very small number of patients (0.3 to 1.0%).

4.9 Overdose

To date there has been limited experience with overdose of fluvastatin. Specific treatment is not available for Lescol/Lescol XL overdose. Should an overdose occur, the patient should be treated symptomatically

and supportive measures instituted, as required. Liver function tests and serum CK levels should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10A A04

Fluvastatin, a fully synthetic cholesterol-lowering agent, is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Fluvastatin exerts its main effect in the liver and is mainly a racemate of the two erythro enantiomers of which one exerts the pharmacological activity. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction in the plasma cholesterol concentration.

Lescol/Lescol XL reduces total-C, LDL-C, Apo B, and triglycerides, and increases HDL-C in patients with hypercholesterolaemia and mixed dyslipidaemia.

In 12 placebo-controlled studies in patients with Type IIa or IIb hyperlipoproteinaemia, Lescol alone was administered to 1,621 patients in daily dose regimens of 20 mg, 40 mg and 80 mg (40 mg twice daily) for at least 6 weeks duration. In a 24-week analysis, daily doses of 20 mg, 40 mg and 80 mg produced dose-related reductions in total-C, LDL-C, Apo B and in triglycerides and increases in HDL-C (see Table 2).

Lescol XL was administered to over 800 patients in three pivotal trials of 24 weeks active treatment duration and compared to Lescol 40 mg once or twice daily. Given as a single daily dose of 80 mg, Lescol XL significantly reduced total-C, LDL-C, triglycerides (TG) and Apo B (see Table 2).

Therapeutic response is well established within two weeks, and a maximum response is achieved within four weeks. After four weeks of therapy, the median decrease in LDL-C was 38% and at week 24 (endpoint) the median LDL-C decrease was 35%. Significant increases in HDL-C were also observed.

Table 2 Median percent change in lipid parameters from baseline to week 24 Placebo-controlled studies (Lescol) and active-controlled trials (Lescol XL)

	Total-C		TG		LDL-C		Apo B		HDL-C	
Dose	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**
All patients										
Lescol 20 mg[1]	747	-17	747	-12	747	-22	114	-19	747	+3
Lescol 40 mg[1]	748	-19	748	-14	748	-25	125	-18	748	+4
Lescol 40 mg twice daily[1]	257	-27	257	-18	257	-36	232	-28	257	+6
Lescol XL 80 mg[2]	750	-25	750	-19	748	-35	745	-27	750	+7
Baseline TG ≥ 200 mg/dl										
Lescol 20 mg[1]	148	-16	148	-17	148	-22	23	-19	148	+6
Lescol 40 mg[1]	179	-18	179	-20	179	-24	47	-18	179	+7
Lescol 40 mg twice daily[1]	76	-27	76	-23	76	-35	69	-28	76	+9
Lescol XL 80 mg[2]	239	-25	239	-25	237	-33	235	-27	239	+11

[1] Data for Lescol from 12 placebo-controlled trials
[2] Data for Lescol XL 80 mg tablet from three 24-week controlled trials

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of fluvastatin on coronary atherosclerosis was assessed by quantitative coronary angiography in male and female patients (35 to

75 years old) with coronary artery disease and baseline LDL-C levels of 3.0 to 4.9 mmol/l (115 to 190 mg/dl). In this randomised, double-blind, controlled clinical study, 429 patients were treated with either fluvastatin 40 mg/day or placebo. Quantitative coronary angiograms were evaluated at baseline and after 2.5 years of treatment and were evaluable in 340 out of 429 patients. Fluvastatin treatment slowed the progression of coronary atherosclerosis lesions by 0.072 mm (95% confidence intervals for treatment difference from −0.1222 to −0.022 mm) over 2.5 years as measured by change in minimum lumen diameter (fluvastatin −0.028 mm vs. placebo −0.100 mm). No direct correlation between the angiographic findings and the risk of cardiovascular events has been demonstrated.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE; i.e. cardiac death, non-fatal myocardial infarction and coronary revascularisation) was assessed in patients with coronary heart disease who had first successful percutaneous coronary intervention. The study included male and female patients (18 to 80 years old) and with baseline total-C levels ranging from 3.5 to 7.0 mmol/l (135 to 270 mg/dl).
In this randomised, double-blind, placebo-controlled trial fluvastatin (n=844), given as 80 mg daily over 4 years, significantly reduced the risk of the first MACE by 22% (p=0.013) as compared to placebo (n=833). The primary endpoint of MACE occurred in 21.4% of patients treated with fluvastatin vs 26.7% of patients treated with placebo (absolute risk difference: 5.2%; 95% CI: 1.1 to 9.3). These beneficial effects were particularly noteworthy in patients with diabetes mellitus and in patients with multivessel disease.

Paediatric population
Children and adolescents with heterozygous familial hypercholesterolaemia
The safety and efficacy of Lescol and Lescol XL in children and adolescent patients aged 9-16 years of age with heterozygous familial hypercholesterolaemia has been evaluated in 2 open-label, uncontrolled clinical trials of 2 years' duration. 114 patients (66 boys and 48 girls) were treated with fluvastatin administered as either Lescol capsules (20 mg/day to 40 mg twice daily) or Lescol XL 80 mg prolonged-release tablets once daily using a dose-titration regimen based upon LDL-C response.

The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level > 90th percentile for age and one parent with primary hypercholesterolaemia and either a family history of premature ischaemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dl equivalent to 5.8 mmol/l (range: 137-354 mg/dl equivalent to 3.6-9.2 mmol/l). All patients were started on Lescol capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg twice daily) to achieve an LDL-C goal of 96.7 to 123.7 mg/dl (2.5 mmol/l to 3.2 mmol/l).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C > 190 mg/dl (equivalent to 4.9 mmol/l) or LDL-C > 160 mg/dl (equivalent to 4.1 mmol/l) and one or more risk factors for coronary heart disease, or LDL-C > 160 mg/dl (equivalent to 4.1 mmol/l) and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dl equivalent to 5,8 mmol/l (range: 148-343 mg/dl equivalent to 3.8-8.9 mmol/l). All patients were started on Lescol capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (Lescol 80 mg XL tablet) to achieve an LDL-C goal of < 130 mg/dl (3.4 mmol/l). 70 patients were pubertal or postpubertal (n=69 evaluated for efficacy).

In the first study (in prepubertal boys), Lescol 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 21% and 27%, respectively. The mean achieved LDL-C was 161 mg/dl equivalent to 4.2 mmol/l (range: 74-336 mg/dl equivalent 1.9-8.7 mmol/l). In the second study (in pubertal or postpubertal girls and boys), Lescol 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-C was 159 mg/dl equivalent to 4.1 mmol/l (range: 90-295 mg/dl equivalent to 2.3-7.6 mmol/l).

The majority of patients in both studies (83% in the first study and 89% in the second study) were titrated to the maximum daily dose of 80 mg. At study endpoint, 26 to 30% of patients in both studies achieved a targeted LDL-C goal of < 130 mg/dl (3.4 mmol/l).

5.2 Pharmacokinetic properties

Absorption
Fluvastatin is absorbed rapidly and completely (98%) after oral administration of a solution to fasted volunteers. After oral administration of Lescol XL, and in comparison with the capsules, the absorption rate of fluvastatin is almost 60% slower while the mean residence time of fluvastatin is increased by approximately 4 hours. In a fed state, the substance is absorbed at a reduced rate,

Distribution
Fluvastatin exerts its main effect in the liver, which is also the main organ for its metabolism. The absolute bioavailability assessed from systemic blood concentrations is 24%. The apparent volume of distribution (Vz/f) for the drug is 330 litres. More than 98% of the circulating drug is bound to plasma proteins, and this binding is not affected either by the concentration of fluvastatin, or by warfarin, salicylic acid or glyburide.

Biotransformation
Fluvastatin is mainly metabolised in the liver. The major components circulating in the blood are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically. There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation and thus fluvastatin metabolism is relatively insensitive to CYP450 inhibition.

Fluvastatin inhibited only the metabolism of compounds that are metabolised by CYP2C9. Despite the potential that therefore exists for competitive interaction between fluvastatin and compounds that are CYP2C9 substrates, such as diclofenac, phenytoin, tolbutamide and warfarin, clinical data indicate that this interaction is unlikely.

Elimination
Following administration of 3H-fluvastatin to healthy volunteers, excretion of radioactivity is about 6% in the urine and 93% in the faeces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. The plasma clearance (CL/f) for fluvastatin in man is calculated to be 1.8 ± 0.8 l/min. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 80 mg daily. Following oral administration of 40 mg Lescol, the terminal disposition half-life for fluvastatin is 2.3 ± 0.9 hours.

Characteristics in patients
Plasma concentrations of fluvastatin do not vary as a function of either age or gender in the general population. However, enhanced treatment response was observed in women and in elderly people. Since fluvastatin is eliminated primarily via the biliary route and is subject to significant presystemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency (see sections 4.3 and 4.4).

Children and adolescents with heterozygous familial hypercholesterolaemia
No pharmacokinetic data in children are available.

5.3 Preclinical safety data

The conventional studies, including safety pharmacology, genotoxicity, repeated dose toxicity, carcinogenicity and toxicity on reproduction studies did not indicate other risks for the patient than those expected due to the pharmacological mechanism of action. A variety of changes were identified in toxicity studies that are common to HMG-CoA reductase inhibitors. Based on clinical observations, liver function tests are already recommended (see section 4.4). Further toxicity seen in animals was either not relevant for human use or occurred at exposure levels sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Despite the theoretical considerations concerning the role of cholesterol in embryo development, animal studies did not suggest an embryotoxic and teratogenic potential of fluvastatin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed Nationally]

6.2 Incompatibilities

Not applicable.

[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 <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex 1 - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Lescol and associated names (see Annex I) 20 mg capsules, hard
Lescol and associated names (see Annex I) 40 mg capsules, hard
Lescol XL and associated names (see Annex I) 80 mg prolonged-release tablets

[See Annex I – To be completed Nationally]

Fluvastatin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 20 mg fluvastatin
Each capsule contains 40 mg fluvastatin
Each tablet contains 80 mg fluvastatin

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For 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

[To be completed Nationally]

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 1 - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed Nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Lescol and associated names (see Annex I) 20 mg capsules, hard
Lescol and associated names (see Annex I) 40 mg capsules, hard
Lescol XL and associated names (see Annex I) 80 mg prolonged-release tablets

Fluvastatin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex 1 - To be completed nationally]

3. EXPIRY DATE

[To be completed Nationally]

4. BATCH NUMBER

[To be completed Nationally]

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Lescol and associated names (see Annex I) 20 mg capsules, hard
Lescol and associated names (see Annex I) 40 mg capsules, hard
Lescol XL and associated names (see Annex I) 80 mg prolonged-release tablets

[See Annex 1 - To be completed nationally]

Fluvastatin

Read all of this leaflet carefully before you start using 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 LESCOL/LESCOL XL IS AND WHAT IT IS USED FOR

Lescol/Lescol XL contains the active fluvastatin sodium which belongs to a group of medicines known as statins, which are lipid-lowering medicines: they lower the fat (lipids) in your blood. They are used in patients whose conditions cannot be controlled by diet and exercise alone.

- Lescol/Lescol XL is a medicine used to **treat raised levels of fats in the blood in adults,** in particular total cholesterol and so called "bad" or LDL cholesterol, which is associated with an increased risk of heart disease and stroke.
  - in adult patients with high blood levels of cholesterol
  - in adult patients with high blood levels of both cholesterol and triglycerides (another sort of blood lipid)

- Your doctor can also prescribe Lescol/ Lescol XL to prevent further serious cardiac events (e.g. heart attack) in patients after they already went through a heart catheterisation, with an intervention in the heart vessel.

2. BEFORE YOU TAKE LESCOL/LESCOL XL

Follow all instructions given to you by your doctor carefully. They may differ from the information contained in this leaflet.

Read the following explanations before you take Lescol/Lescol XL.

Do not take Lescol/Lescol XL

- if you are allergic (hypersensitive) to fluvastatin or any of the other ingredients of Lescol/Lescol XL listed in section 6 of this leaflet.
- if you currently have liver problems, or if you have unexplained, persistently high level of certain liver enzymes (transaminases).
- if you are pregnant or breast-feeding (see "pregnany and breast-feeding").

If any of these apply to you, do not take Lescol/ Lescol XL and tell your doctor.

Take special care with Lescol/Lescol XL
- if you previously had a liver disease. Liver function tests will normally be done before you start Lescol/Lescol XL, when your dose is increased and at various intervals during treatment to check for side effects.
- if you have a kidney disease.
- if you have a thyroid disease (hypothyroidism).
- if you have a medical history of muscle diseases yourself or in your family.
- if you had muscle problems with another lipid-lowering medicine.
- if you regularly drink large amounts of alcohol.

Check with your doctor or pharmacist before taking Lescol/Lescol XL:
- if you have severe respiratory failure

If any of these apply to you, **tell your doctor before you take** Lescol/Lescol XL. Your doctor will take a blood test before prescribing Lescol/Lescol XL.

Lescol/Lescol XL and people over 70 years
If you are over 70 years your doctor may want to check if you have risk factors for muscular diseases. You may need specific blood tests.

Lescol/Lescol XL and children/adolescents
Lescol/Lescol XL has not been investigated and is not intended for the use in children below 9 years. For dose information in children and adolescents over 9 years, see section 3.

There is no experience with the use of Lescol in combination with nicotinic acid, cholestyramine or fibrates in children and adolescents.

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.
Lescol/Lescol XL can be taken on its own or with other cholesterol-lowering medicines prescribed by your doctor.

After intake of a resin, e.g. cholestyramine (primarily used to treat high cholesterol) wait at least 4 hours before taking Lescol/Lescol XL.

Tell your doctor and pharmacist if you are taking any of the following:
- Ciclosporin (a medicine used to suppress the immune system).
- Fibrates (e.g. gemfibrozil), nicotinic acid or bile acid sequestrants (medicines used to lower bad cholesterol levels).
- Fluconazole (a medicine used to treat fungal infections).
- Rifampicin (an antibiotic).
- Phenytoin (a medicine used to treat epilepsy).
- Oral anticoagulants like warfarin (medicines used to reduce blood clotting).
- Glibenclamide (a medicine used to treat diabetes).
- Colchicines (used to treat gout).

Taking Lescol/Lescol XL with food and drink
You can take Lescol/Lescol XL with or without food.

Pregnancy and breast-feeding
Do not take Lescol / Lescol XL if you are pregnant or breast-feeding as the active ingredient may lead to harm to your unborn child, and it is not known whether the active ingredient is excreted in human breast milk. If you are pregnant, consult your doctor or pharmacist before taking Lescol/Lescol XL. Use reliable contraception for the whole time that you are taking Lescol / Lescol XL.

If you become pregnant while taking this medicine, stop taking Lescol/Lescol XL and see your doctor.

Driving and using machines
There is no information on the effects of Lescol/Lescol XL on your ability to drive and use machines.

Important information about some of the ingredients of Lescol/Lescol XL
[To be completed nationally]

3. HOW TO TAKE LESCOL/LESCOL XL

Follow your doctor's instructions carefully. Do not exceed the recommended dose.

Your doctor will recommend you to follow a low-cholesterol diet. Stay on this diet while taking Lescol/Lescol XL.

How much Lescol/ Lescol XL to take

- The dose range for adults is 20 to 80 mg per day and depends on the extent of cholesterol lowering which needs to be achieved. Dose adjustments may be made by your doctor at 4-week or longer intervals.
- For children (aged 9 years and older) the usual starting dose is 20 mg per day. The maximum daily dose is 80 mg. Dose adjustments may be made by your doctor at 6-week intervals.

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

When to take Lescol/ Lescol XL
If you are taking Lescol, take your dose in the evening or at bedtime.
If you are taking Lescol twice per day, take one capsule in the morning and one in the evening or at bedtime.
If you are taking Lescol XL tablets you can take your dose at any time of the day.
Lescol and Lescol XL can be taken with or without meals. Swallow whole with a glass of water.

If you take more Lescol/Lescol XL than you should
If you have accidentally taken too much Lescol/Lescol XL, talk to your doctor straight away. You may need medical attention.

If you forget to take Lescol/Lescol XL
Take one dose as soon as you remember. However, do not take it if there is less than 4 hours before your next dose. In this case take your next dose at the usual time.
Do not take a double dose to make up for the one that you missed.

If you stop taking Lescol/Lescol XL
To maintain the benefits of your treatment, do not stop taking Lescol/ Lescol XL unless your doctor tells you to. You must continue to take Lescol/Lescol XL as directed to keep the levels of your 'bad' cholesterol

down. Lescol/ Lescol XL will not cure your condition but it does help control it. Your cholesterol levels need to be checked regularly to monitor your progress.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lescol/Lescol XL can cause side effects, although not everybody gets them.
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 rare or very rare effects could be serious: get medical help immediately.
- if you have unexplained muscle pain, tenderness or weakness. These might be early signs of a potentially severe muscle degradation. This can be avoided if your doctor stops your treatment with fluvastatin as quickly as possible. These side effects have also been found with similar medicines of this class (statins).
- if you have unusual tiredness or fever, yellowing of the skin and eyes, dark coloured urine (signs of hepatitis).
- if you have signs of skin reactions such as skin rash, hives, redness, itching, swelling of the face, eyelids, and lips.
- if you have skin swelling, difficulty in breathing, dizziness (signs of severe allergic reaction).
- if you bleed or bruise more easily than normal (signs of decreased number of blood platelets).
- if you have red or purple skin lesions (signs of blood vessel inflammation).
- if you have red blotchy rash mainly on the face which may be accompanied by fatigue, fever, nausea, loss of appetite (signs of lupus erythematous-like reaction).
- if you have severe upper stomach pain (signs of inflamed pancreas).

If you experience any of these, tell your doctor straight away.

Other side effects: tell your doctor if they worry you.
Common:
Difficulty in sleeping, headache, stomach discomfort, abdominal pain, nausea.
Very rare:
Tingling or numbness of the hands or feet, disturbed or decreased sensibility.

Other possible side effects
- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual difficulties
- Depression
- Breathing problems including persistent cough and/or shortness of breath or fever

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

5. HOW TO STORE LESCOL/LESCOL XL

[To be completed nationally]
Keep Lescol/Lescol XL out of the reach and sight of children.

Do not use Lescol/Lescol XL after the expiry date which is stated on the carton and blister after [To be completed nationally].
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 Lescol/Lescol XL contains

- The active substance is fluvastatin sodium
  Each Lescol 20 mg capsule contains 21.06 mg fluvastatin sodium equivalent to 20 mg fluvastatin free acid.
  Each Lescol 40 mg capsule contains 42.12 mg fluvastatin sodium equivalent to 40 mg fluvastatin free acid.
  Each Lescol XL 80 mg tablet contains 84.24 mg fluvastatin sodium equivalent to 80 mg fluvastatin free acid.
- The other ingredients of Lescol 20 mg capsules are:

[To be completed nationally]

What Lescol/Lescol XL looks like and contents of the pack
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:
[See Annex I - To be completed nationally]

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

20 mg and 40 mg capsules

Member State	Medicinal Product
Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Greece, Iceland, Ireland, Italy, Malta, Norway, Netherlands, Poland, Portugal, Romania, Slovak Republic, Spain, Sweden, United Kingdom	Lescol
Germany, Luxembourg	Locol
Austria	Fluvastatin Novartis
France	Fractal
Germany	Cranoc
Italy	Lipaxan, Primesin, Fluvastatina
Portugal	Cardiol, Canef
Spain	Liposit, Vaditon, Digaril, Lymetel

40 mg capsules

Member State	Medicinal Product
Bulgaria, Estonia, Hungary, Slovenia	Lescol

80 mg prolonged-release tablets

Member State	Medicinal Product
Estonia, Bulgaria, Cyprus, Czach Republic, Greece,	Lescol XL

Hungary, Ireland, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, United Kingdom	
Demark, Finland, Iceland, Norway, Sweden	Lescol Depot
Austria, Germany	Fluvastatin Novartis
Austria	Lescol MR
Belgium	Lescol Exel
France	Lescol LP
Germany, Luxembourg	Locol
Italy	Lescol, Lipaxin, Primesin
Portugal	Cardiol XL, Canef
Spain	Lescol Prolib, Liposit Prolib, Vaditon Prolib, Digaril Prolib

This leaflet was last approved in

[To be completed nationally]