SCHEDULING STATUS S4

PROPRIETARY NAMES AND DOSAGE FORMS
LESCOL® 20 mg capsule
LESCOL® 40 mg capsule
LESCOL XL® film-coated tablet

COMPOSITION

LESCOL 20 mg:	Each capsule contains 20 mg fluvastatin as fluvastatin sodium.
LESCOL 40 mg:	Each capsule contains 40 mg fluvastatin as fluvastatin sodium.
LESCOL XL:	Each tablet contains 80 mg fluvastatin as fluvastatin sodium.

PHARMACOLOGICAL CLASSIFICATION
A 7.5 Serum-cholesterol reducers.

PHARMACOLOGICAL ACTION
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 results of these mechanisms are a reduction of the plasma cholesterol concentration.

In patients with hypercholesterolemia, treatment with LESCOL/LESCOL XL reduced total-C, LDL-C and apo-lipoprotein B. Fluvastatin also variably reduces triglycerides whereas an increase in HDL-C is modest and variable.

Pharmacokinetics:
Absorption:
Fluvastatin is absorbed rapidly and completely (98 %) after oral administration of a solution to fasted volunteers. The absolute oral bioavailability assessed from systemic blood concentrations is 24 % for the LESCOL capsules. The systemic exposure with LESCOL XL 80 was approximately 25 % lower to that of the capsules. After oral administration of LESCOL XL 80, and in comparison with the capsules, the absorption rate of fluvastatin is about 60 % slower compared to LESCOL capsules while the mean residence time of fluvastatin is increased by approximately 4 hours. In fed state, the drug 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 apparent volume of distribution (V_z/f) for the drug is 330 L. More than 98 % of the circulating drug is bound to plasma proteins, and this binding is unaffected neither by the concentration of fluvastatin, nor by warfarin, salicylic acid, and glyburide.

Metabolism:
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. The hepatic pathways of fluvastatin metabolism in humans have been completely elucidated. There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation and thus fluvastatin metabolism is relatively insensitive to CYP450 inhibition, a major cause of adverse drug-drug interactions.

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 of fluvastatin is 2,3 ± 0,9 hours.

Results from an overnight pharmacokinetic evaluation following steady-state administration of LESCOL 20 mg and 40 mg with the evening meal or 4 hours after the evening meal for fifteen weeks showed that administration of fluvastatin sodium with the evening meal results in a two-fold decrease in C_{max} and more than a two-fold increase in t_{max} as compared to patients receiving the drug 4 hours after the evening meal. No significant difference in AUC was observed between the two treatment groups, and there were no differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal.

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. Due to their generally smaller body weight, young female patients show higher fluvastatin concentrations after administration of 20 to 40 mg compared to young males.

Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

INDICATIONS
Adults:
LESCOL/LESCOL XL is indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels and for the increase of HDL-C in adults with primary hypercholesterolemia and mixed dyslipidaemia (Fredrickson Types IIa and IIb).

Paediatric population:
LESCOL/LESCOL XL is indicated as an adjunct to diet for the reduction of elevated total-C, LDL-C and apo B levels in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia.

LESCOL/LESCOL XL is also indicated to slow the progression of coronary atherosclerosis in adults with primary hypercholesterolaemia and concomitant coronary heart disease who do not adequately respond to dietary control.

To reduce the risk of undergoing coronary revascularisation procedures in patients with multivessel disease.

CONTRA-INDICATIONS

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. HMG-CoA reductase inhibitors are therefore, contra-indicated during pregnancy, in nursing mothers, and in women of childbearing potential not taking adequate contraceptive precautions. If a patient becomes pregnant while taking this class of drug, therapy should be discontinued.

- 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.
- During pregnancy and lactation (see *Pregnancy and lactation*).
- No data are available for the use of LESCOL/LESCOL XL in patients with a rare condition known as homozygous familial hypercholesterolemia.

As there is no experience with LESCOL/LESCOL XL in patients with severe renal insufficiency

(creatinine >260 mmol/L i.e. creatinine clearance <30 ml/min), its use cannot be recommended in this patient population.

WARNINGS

Laboratory findings:
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (1-2 %). Marked elevations of levels to more than 5x ULN developed in a very small number of patients (0,3-1,0 %).

Liver function:
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, therapy should be discontinued. Possibly drug-related hepatitis has been observed and 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:
In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values**,** myopathy, myositis or rhabdomyolyisis 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 and LESCOL/LESCOL XL should be stopped until it is ascertained that the symptoms are not related to elevated CK values.

Creatine kinase measurement:
There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase 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 the treatment:
Medical practitioners should prescribe LESCOL/LESCOL XL with caution in patients with pre-disposing factors for rhabdomyolysis and its complications. A creatine kinase level should be measured before starting LESCOL/LESCOL XL 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 disposing 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 upper limit of normal {ULN}), levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated (>5xULN) at baseline, treatment should not be started.

Whilst on treatment:
If muscular symptoms like pain, weakness or cramps occur in patients receiving LESCOL/LESCOL XL, their CK-levels should be measured. Treatment should be stopped, if these levels are found to be significantly elevated (>5xULN).

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

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

LESCOL/LESCOL XL therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis.

The risk of myopathy has been reported to be increased in patients receiving immunosuppressive medicines (including ciclosporin), fibrates, nicotinic acid, fluconazole or erythromycin together with HMG-CoA reductase inhibitors. Cases of myopathy have been reported post-marketing for concomitant administration of LESCOL/LESCOL XL with ciclosporin and fluvastatin with colchicine. LESCOL/LESCOL XL should be used with caution in patients receiving such concomitant medication (see *Interactions*). The combined use of the HMG-COA reductase inhibitors and fibrates should be avoided.

Paediatric population:
In patients aged <18 years, efficacy and safety have not been studied for treatment periods longer than two years.

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

INTERACTIONS
Food Interactions:
There are no apparent differences in the lipid-lowering effects of LESCOL/LESCOL XL when administered with the evening meal or 4 hours after the evening meal.
Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, LESCOL/LESCOL XL is not expected to interact with grapefruit juice.

Drug interactions:
Effect of other drugs on LESCOL/LESCOL XL:
Fibric acid derivatives (fibrates) and niacin (nicotinic acid):
Concomitant administration of LESCOL/LESCOL XL with bezafibrate, gemfibrozil, ciprofibrate or niacin (nicotinic acid) has no clinically relevant effect on bioavailability of LESCOL/LESCOL XL or the other lipid-lowering agent. However, since an increased risk of myopathy has been observed in patients receiving HMG-CoA reductase inhibitors together with any of these molecules, these combinations should be used with caution (see *Warnings* and *Contra-indication*).

Itraconazole and erythromycin:
Concomitant administration of LESCOL/LESCOL XL with the potent cytochrome P450 (CYP3A4) 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.

Fluconazole:
Administration of LESCOL/LESCOL XL 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 LESCOL/LESCOL XL is administered concomitantly with fluconazole.

Ciclosporin:

Studies in renal transplant patients receiving ciclosporin in addition to LESCOL/LESCOL XL, indicate that the bioavailability (i.e. AUC) of fluvastatin (20 mg/day) is increased 1,9 fold compared to historical controls treated with the same dosage of fluvastatin alone. In clinical trials, stable regimens of ciclosporin in combination with dosages of fluvastatin 20-40 mg/day have been well tolerated. The results from another study wherein LESCOL XL (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 by 2 fold compared to historical data in healthy subjects**.** Although these increases in fluvastatin levels were not significant, this combination should be used with caution.

Bile-acid-sequestering agents:
Administration of LESCOL/LESCOL XL concomitantly with, or up to 4 hours after cholestyramine results in fluvastatin decreases of more than 50 % for AUC and 50-80 % for C_{max}, however administration of LESCOL/LESCOL XL 4 hours after cholestyramine results in a clinically significant additive effect compared to that achieved with either drug alone. LESCOL/LESCOL XL should therefore be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding of the resin.

Rifampicin:
Administration of LESCOL/LESCOL XL 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 LESCOL/LESCOL XL dosage may be warranted to ensure a satisfactory reduction in lipid levels.

Histamine H_2-receptor antagonists and proton pump inhibitors:
Concomitant administration of LESCOL/LESCOL XL with cimetidine, ranitidine, or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance. While additional interaction studies have not been performed, it is expected that other H_2-receptor antagonists/proton pump inhibitors are unlikely to affect the bioavailability of fluvastatin.

Phenytoin:
The minimal effect of phenytoin on fluvastatin pharmacokinetics indicates that dosage adjustment of LESCOL/LESCOL XL is not warranted when co-administered with phenytoin.

Cardiovascular agents:
No clinically significant pharmacokinetic interactions occur when LESCOL/LESCOL XL is concomitantly administered with propranolol, digoxin, or losartan or amlodipine. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when LESCOL/LESCOL XL is concomitantly administered with these agents.

Effect of *LESCOL/LESCOL XL* on other drugs:
Several *in vitro* studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. 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 and tolbutamide, clinical data indicate that this interaction is unlikely.

Ciclosporin:
Both LESCOL 40 mg (immediate release fluvastatin) and LESCOL XL had no effect on ciclosporin bioavailability when co-administered (see also *Effects of other drugs on* LESCOL/LESCOL XL), however LESCOL/LESCOL XL bioavailabilty is doubled (see *Warnings*).

Colchicine:
No information is available on the pharmacokinetic interaction between fluvastatin and colchicine. However, myotoxicity including muscle pain and weakness and rhabdomyolysis, have been reported with concomitant administration of colchicine.

Phenytoin:
The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with LESCOL/LESCOL XL are relatively small and not clinically significant. Thus, routine monitoring of phenytoin plasma levels is sufficient during co-administration with LESCOL/LESCOL XL.

Warfarin and other coumarin derivatives:
Increases in INR and isolated events of bleeding. More frequent monitoring is recommended, especially when LESCOL/LESCOL XL treatment is initiated, discontinued, or the dosage changed in patient receiving warfarin or other coumarin derivatives.

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 LESCOL/LESCOL XL 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 t½ of glibenclamide 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 LESCOL/LESCOL XL should continue to be monitored appropriately when their LESCOL dose is increased to 80 mg per day, as safety with this combination is not known.

PREGNANCY AND LACTATION
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 contra-indicated during pregnancy.

Women of childbearing potential have to use effective contraception. If a patient becomes pregnant while taking LESCOL/LESCOL XL, therapy should be discontinued.

Lactation:
LESCOL/LESCOL XL is contra-indicated in nursing mothers.

DOSAGE AND DIRECTIONS FOR USE
Prior to initiating LESCOL/LESCOL XL, the patient should be placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsule LESCOL 40 mg once daily) or 80 mg (1 tablet LESCOL XL 80 mg once daily or one capsule LESCOL 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule LESCOL 20 mg) may be adequate in mild cases. Starting doses should be individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of LESCOL/LESCOL XL is maintained with prolonged administration.

LESCOL/LESCOL XL is efficacious in monotherapy or in combination with bile acid sequestrants or other resins. Data exist to support the efficacy and safety of LESCOL/LESCOL XL in combination with nicotinic acid and cholestyramine (see *Interactions*).

Paediatric population:
Prior to initiating treatment with LESCOL/LESCOL XL, the patient should be placed on a standard

cholesterol-lowering diet for 6 months. Dietary therapy should be continued during treatment.

The recommended starting once daily dose is 40 mg (1 capsule LESCOL 40 mg) or 80 mg (1 tablet LESCOL XL 80 mg or two capsules LESCOL 40 mg). The dose of 20 mg fluvastatin (1 capsule LESCOL 20 mg) may be adequate in mild cases. Starting doses should be individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

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

Patients with impaired liver function:
LESCOL/LESCOL XL is contra-indicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see *Contra-indications*).

Elderly and young patients:
In clinical studies with LESCOL/LESCOL XL efficacy and tolerability were demonstrated in age groups both above and under 65 years. In the elderly group (>65 years), there was no evidence of reduced tolerability. Therefore there is no need to adjust dose based on age.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
Adverse reactions 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 ranked in order of decreasing seriousness.

Since LESCOL/LESCOL XL is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

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

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 (See Warnings):
Rare: Myalgia, muscle weakness, myopathy.
Very rare: Rhabdomyolysis, myositis, lupus erythematosus-like reactions

Laboratory findings:
Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (1-2 %).

Marked elevations of levels to more than 5x ULN developed in a very small number of patients (0,3-1,0 %).

Paediatric population:
The safety profile of LESCOL/LESCOL XL in children and adolescents with heterozygous familial hypercholesterolemia assessed in two clinical trials was similar to the one observed in adults. In both clinical trials, all children and adolescents continued with their normal growth and sexual maturation.

Patients with impaired liver and kidney function:
Since fluvastatin is eliminated primarily via the biliary route and is subject to significant pre-systemic metabolism, the potential exists for drug accumulation in patients with hepatic insufficiency.

LESCOL/LESCOL XL is contra-indicated in patients with active liver disease or unexplained persisted elevation in serum transaminases (see *Contra-indications*).

Fluvastatin is cleared by the liver, with less than 6 % of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remains unchanged in patients with mild to severe renal insufficiency. No dose adjustments are therefore necessary in these patients.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
In a placebo-controlled study including 40 hypercholesterolaemic patients, doses up to 320 mg/day (n=7 per dose group) administered as LESCOL XL 80 mg tablets over two weeks were well tolerated. No specific recommendations concerning the treatment of an overdosage can be made. Should an overdose occur, it should be treated symptomatically and supporting measures should be undertaken as required.

IDENTIFICATION
LESCOL® 20 mg capsule: A No. 3 hard gelatin capsule with a strong reddish brown opaque cap and pale yellow opaque body with XU 20 mg imprinted in red.

LESCOL® 40 mg capsule: A No. 1 hard gelatin capsule with a strong reddish brown opaque cap and a moderate orange yellow opaque body with XU 40mg imprinted in red.

LESCOL XL® film-coated tablet: Yellow, round, slightly biconvex, bevelled edged film-coated tablet, with “LE” imprinted on the one side and “NVR” on the other side.

PRESENTATION
LESCOL® capsules: Alu/alu blister packs –28 capsules per pack.
LESCOL XL® film-coated tablets**:** PA/Al/PVC aluminium foil blister packs of 28.
The blister strips are packed in a printed cardboard box.

STORAGE INSTRUCTIONS
LESCOL® capsules:
Store in a cool dry place below 25 °C.
KEEP OUT OF REACH OF CHILDREN.
LESCOL XL® film-coated tablets**:**
Store in a cool dry place below 30 °C.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

LESCOL® 20 mg capsule	28/7.5/0159
LESCOL® 40 mg capsule	28/7.5/0160
LESCOL XL® film-coated tablet	35/7.5/0327

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION
NOVARTIS SOUTH AFRICA (PTY) LTD
Magwa Crescent West
Waterfall City, Jukskei View
Johannesburg 2090
South Africa

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