CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-192

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA: 21-192
Name: Lescol XL® 80 mg. Tablets (fluvastatin sodium)
Sponsor: Novartis
Submission Type: NDA
Reviewer: Paul L. Hepp, Pharm.D.

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

TABLE OF CONTENTS

Synopsis

The sponsor has submitted this NDA in support of Lescol XL 80 mg. Tablets (——— tablet). The proposed labeling for this product is for one 80 mg tablet to be taken in the evening. Fluvastatin Immediate release capsules are currently approved in the United States. Six controlled clinical studies have been submitted as well as four human Pharmacokinetic/Biopharmaceutic studies and CMC information. The clinical studies utilized the to be marketed formulation and there is no bioequivalence issue. The sponsor indicates that HFD-510 had agreed that no additional preclinical information beyond that which was submitted for NDA 20-261 (Lescol Capsules) would be required.

Based on study W251, Lescol XL 80 mg. tablets (— to be marketed tablet formulation) were shown to have significantly lower systemic availability under fed and fasted conditions as compared to immediate release fluvastatin capsules. There was little difference in bioavailability seen for the to be marketed Lescol XL when administered with a low fat meal or two and a half hours after a meal. This study also supported a finding of a saturable first pass effect for fluvastatin.

A steady state safety / tolerability and pharmacokinetics study (W253) utilizing a slower (— tablet) releasing than the to be marketed Lescol XL fluvastatin tablet, revealed dose and time dependent pharmacokinetic nonlinearity over the 80 to 640 mg. dosage range. Although this study did not use the to be marketed Lescol XL tablet — tablet), it is useful as it predicts that the to be marketed Lescol XL tablet with more rapid release will probably also have dose and time dependent pharmacokinetic nonlinearity, and also perhaps greater systemic exposure for the to be marketed Lescol XL tablet than for the slower releasing tablet used in this study. The safety and tolerability results obtained from this study may not be predictive of those of the to be marketed Lescol XL tablet since the tablet utilized in this study would be expected to give a lower systemic exposure as compared to the to be marketed Lescol XL tablet (faster release leading to greater first pass saturation). Single dose study W251 indicates that the — to be marketed tablet differs from the — tablet (63% difference in AUC, 104% difference in Cmax, and 38% difference in Tmax). An appropriate steady state comparative bioavailability study where the to be marketed 80 mg Lescol tablet dosed every evening is compared to the approved 40 mg b.i.d. immediate release capsule regimen is being recommended to be conducted on a phase IV basis as multiple dose study 253 did not include an appropriate reference and the correct to marketed product. This study will define the yet unstudied multiple dose pharmacokinetic performance of the to be marketed 80 mg Lescol XL tablet. This study will also allow for comparison of the parameters of Cmax, Cmin, AUC (exposure), and fluctuation between the approved product/regimen (40 mg IR capsule, b.i.d) and the to be marketed 80 mg Lescol XL tablet regimen over the dosage interval. Finally, this study will fulfill the regulatory requirement for such a study as called for in 21 CFR 320.25(f).

Based on the results of a high fat meal vs fasting study (W351), the to be marketed Lescol XL tablets were shown to have high variability in systemic bioavailability, especially when taken with the meal. Additionally, the study revealed greater systemic availability and increased Tmax of the Lescol XL tablet with the high fat meal as compared to fasting. The study showed greater systemic availability of the Lescol XL tablet in females than in males. Finally, due to the repeat fasting dose administration design of the study, it was shown that the intrasubject variability (within subject variability) in systemic bioavailability is much less than the intersubject variability in systemic bioavailability for the Lescol XL tablet.

A dissolution method which appears to be appropriate for the to be marketed Lescol XL tablet was submitted. Based upon the dissolution data on the lots that were used in the bioavailability studies (lots H0501J and T115195) which were also of the same formulation of that lot used in the clinical studies, the ——— sponsor proposed specifications are excessively wide. OCPB recommends a narrowing of the ——— specifications to ———————

A bioavailability study (W252) which utilized fluvastatin product formulations very different than the Lescol XL tablet was not reviewed due to its lack of relevance to Lescol XL.

Labeling consistent with the results of the above reviewed studies has been recommended for the Lescol XL tablets.

RECOMMENDATION

From the Office of Clinical Pharmacology and Biopharmaceutics' standpoint, the application has not met all of the Bioavailability requirements as an acceptable steady state study comparing the 80 mg Lescol XL regimen to the approved 40 mg IR caosule b.i.d. regimen has not been conducted as required under CFR 320.25(f) (Deficiency 1). Further, the proposed dissolution limits are not acceptable (Deficiency 2). If there is adequate safety data to support the use of the Lescol XL tablet over the labeled dosage range, the comparative steady state study bioavailability study can be conducted on a phase 4 basis. Labeling comments have been incorporated into the labeling by the sponsor (Comments 1, 5, 7-9, 13-15, and 17-24). Provided that Deficiency 2 is adequately addressed by the sponsor, and there is adequate safety data to support the use of the Lescol XL tablet, OCPB believes that the application can be approved from our standpoint, and that the comparative steady state bioavailability study (Deficiency 1) can be conducted on a phase 4 basis. Comments 2-4, 10-11, and 16 should be noted by the medical reviewer. This Recommendation, Deficiencies 1 and 2, and Comments 1, 5-9, 11-15, and 17-24 should be conveyed to the sponsor.

DEFICIENCIES

Deficiency

Study W253-Safety and tolerability and pharmacokinetics of fluvastatin MR- ——— tablet

1. An appropriate steady state bioavailability study allowing for comparison of the parameters of Cmax, Cmin, AUC (exposure), and fluctuation over a dosage interval between the approved product/regimen (40 mg IR capsule, b.i.d) and the to be marketed 80 mg Lescol XL tablet dosed every evening has not been conducted. Indeed, no multiple dose study, comparative or otherwise has been conducted on the to be marketed 80 mg Lescol XL tablet. A comparative steady state study is required under 21 CFR 320.25(f).

Study W253 does not meet the requirement for such a study as it did not have an appropriate reference

(ie 40 mg IR capsule, b.i.d) , and the — Lescol XL tablet used in the study is not equivalent to the to be maketed — Lescol XL tablet in terms of rate or extent of absorption ——— Lescol XL tablets differ by 63% in AUC, 104% in Cmax, and 38 % in Tmax under fasting conditions). If there is adequate safety information for the— to be marketed ——. tablet, the missing study could be conducted on a phase IV basis.

Deficiency

In Vitro Dissolution

2. The sponsor's rationale for choosing the apparatus, media, and sampling times appear to be sound.

However, OCPB requires that dissolution specifications be set based on the lots that were used in the bioavailability studies (lots H05018 and T115195) which were also of the same formulation of that used in the clinical studies. Based on this rationale, the 2 and 4 hour sponsor proposed specifications are excessively wide and OCPB recommends a 2 hour specification of ——— and a 4 hour specification of — OCPB agrees with the 0.5 and 8 hour specifications of ———) respectively.

OCPB recommended dissolution limits for fluvastatin sodium MR tablet

Time	Drug released
0.5 hours	
2 hours	
4 hours	
8 hours	

Sponsor Proposed dissolution limits for fluvastatin sodium MR tablet

Time	Drug released
0.5 hours	
2 hours	
4 hours	
8 hours	

COMMENTS

Comments-

Study W251-Relative bioavailability of the fluvastatin 80 MR tablets under 2.5 h post-prandial and fed conditions

1. Labeling should indicate that the ——— formulation resulted in a decreased absorption rate and much lower systemic availability and peak concentrations under fed and 2.5 h post prandial conditions (AHA low fat meals used) as compared to 80 mg of the marketed immediate release capsule (2 x 40 mg) administered under fasted conditions.

Comments-

Study W253-Safety and tolerability and pharmacokinetics of fluvastatin MR- ——— Tablet

2. The study is pilot in nature (small sample size), and therefore these data are limited in providing an assessment of the efficacy of each dose and a dose-response relationship. Additionally, the ——— tablet was used in the study, which differs greatly in its pharmacokinetic performance as compared to the — to be marketed —— tablet formulation. Therefore, the results of the study should not be utilized in assessing the safety, efficacy, pharmacodynamics, or pharmacokinetics of the to marketed ——— formulation.

3. Although this ——— formulation used in this study is not that the same of the ——— tablet to be marketed, the study is still important as predictions regarding the to be marketed ——— tablet can be made based upon this study and study W251. The prediction is that that the nonlinearity will probably be even greater, and exposure levels will probably be greater for the to be marketed —— ——— tablet than for the ——— tablet since it was demonstrated in study W251 that the faster releasing ——— tablet yielded greater exposure than the ——— tablet under both fasting and 2.5 h post-prandial conditions.

Any safety issues based on this study (W253) could therefore be falsely lower than what might be seen with the to be marketed ——— tablet. Therefore, this study should not be relied upon to support the safety of the —to be marketed ——— tablet.

4. The submission notes that the subjects in the 640 mg dose group who experienced increases in LFTs at least 3 times that of the upper limit of normal, all had received co-administration of acetaminophen for fever, body ache, or headache. If this study has not been evaluated by a CDER medical safety evaluator, it should be done for safety in general, and also related to the apparent clinical fluvastatin/acetaminophen interaction.

Comments

Study W351-Effect of food on the bioavailability of fluvastatin MR 80 mg tablet

5. In the submission the sponsor states that fluvastatin concentrations increased gradually with concentrations persisting even at 24 hours, and that this supports the lack of dose dumping of the —— tablet. Looking at the individual subject concentration vs time profiles, it can be seen that in general, concentrations do not increase gradually, but increase rather abruptly. This is especially true for the fed treatment. However, it is difficult to access whether this is due to rapid release, concentration dependent nonlinearity, or a combination of both. Slow release wording in the labeling should not be allowed at the present time.

6. To better assess the issue of in vivo rapid release, deconvolution assessment comparing the fed vs fasted treatments should have been conducted as called for in the Controlled Release Guideline (1984).

7. The high degree of overall variability in the pharmacokinetics of the ——— tablet under fasting conditions, and especially under fed conditions, should be noted in the labeling. The much lower intrasubject variability (variability within a subject) in the pharmacokinetic measures for the —— tablet as compared to the overall variability should also be noted in the labeling.

8. The large increase in systemic availability (AUC and Cmax) for fluvastatin from the ——— tablet after a high fat meal as compared to fasting should be noted in the Oral Absorption text of the labeling as well as in the Pharmacokinetic Table presented in the labeling.

9. The gender effect (increased systemic availability for females) should be noted in the labeling.

10. For purposes of assessing safety and efficacy, it should be pointed out to the medical reviewing staff that food greatly increases the exposure to fluvastatin from the ——— tablet, and that the conditions of dosing in the safety and efficacy studies should be considered in making the assessments for safety and efficacy. If dosing is done under the fasting state, safety may be overestimated for the product if it is taken with food.

11. The report states that based on study W251 where an approved fluvastatin immediate release tablet was one of the treatments, that fluvastatin concentrations seen in the current study with or without food should be considered safe since the concentrations were below those seen from the immediate release dosage form of study W251. The concentrations seen in this study (W353) may be safe, but the reasoning put forth by the sponsor in this instance cannot be used for support. The dose of the immediate release fluvastatin used in study W251, 80 mg, is twice that called for in the approved labeling, and would result in very much higher concentrations than those seen when only a 40 mg immediate release dose is given.

12. No tables of individual subject and mean fluvastatin concentration vs time for the treatments in this study (W351) were included in the submission. This situation hampered the review of the study and should have been submitted. The reviewer would have attempted deconvolution if such information had been readily available.

13. Multiple peaking is observed from the individual subject profiles for both fed and fasting treatments for many of the subjects (about 50%). The timing of some multiple peaking may be consistent with enterohepatic recycling. The sponsor should acknowledge this multiple peaking in the labeling and subsequently offer an explanation for the phenomenon.

GENERAL LABELING COMMENTS

14. The ——— section under Drug Interactions should be removed as ——— is not a good model for drugs metabolised by the microsomal hepatic enzyme system.

15. In the Distribution section of the labeling, it should state that the VDss is 0.35L/Kg rather than ———

16. In the **Dosage and Administration** section of the proposed labeling, it indicates that Lescol or Lescol XL may be taken without regard to food. There is a very large effect of food (50 % increased AUC) for Lescol XL, so this needs to be evaluated by the medical reviewer for safety concerns prior to this statement being allowed in the labeling.

17. Throughout the labeling, material on studies and reported data should include information whether it is related to the IR capsules or the Lescol XL tablets.

18. Under Precautions/Drug Interactions section of the labeling, an intoductory statement indicating that all drug interaction studies listed, utilized the IR capsule form of fluvastatin, and that similar studies were not conducted using the Lescol XL tablet.

19. Under **Precautions/Geriatric Use** in the proposed labeling, it states that ——— ——— This is incorrect and should be removed from the labeling.

20. The following information derived from studies utilizing IV and immediate release radiolabeled fluvastatin formulations was presented in this submission, and should be placed in the Elimination section of the labeling:

Urinary recovery is about 5%. After a radiolabeled dose of fluvastatin, the clearance was 0.8 L/h/kg. Following multiple oral doses of radiolabeled compound, there was no accumulation of fluvastatin; however, there was a 2.3 fold accumulation of total radioactivity.

21. The following pharmacokinetic and metabolism information related to fluvastatin enantiomers appears in this submission and should be included in the Clinical Pharmacology:Pharmacokinetics/Metabolism: Oral Absorption section of the labeling:

Fluvastatin has two optical enantiomers, an active 3R,5S and an inactive 3S,5R form. In vivo studies showed that stereo-selective hepatic binding of the active form occurs during the first pass resulting in a difference in the peak levels of the two enantiomers, with the active to inactive peak

concentrati r: ratio being about 0.7. The approximate ratio of the active to inactive approaches unity after the peak is seen and thereafter the two enantiomers decline with the same half-life. After an intravenous administration, bypassing the first-pass metabolism, the ratios of the enantiomers in plasma were similar throughout the concentration-time profiles.

22. The following in vitro metabolism information related to fluvastatin appears in this submission, and should be included in the Clinical Pharmacology:Pharmacokinetics/Metabolism: Metabolism section of the labeling by the firm:

***In vitro* studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%).**

23. The following pharmacokinetic information related to fluvastatin use in patients with hepatic insufficiency appears in this submission, and should be included in the Clinical Pharmacology: Pharmacokinetics/Metabolism: Special Populations: Hepatic Insufficiency section of the labeling:

Fluvastatin AUC and Cmax values increased by about 2.5 fold in hepatic insufficiency patients. This result was attributed to the decreased presystemic metabolism due to hepatic dysfunction. The enantiomer ratios of the two isomers of fluvastatin in hepatic insufficiency patients were comparable to those observed in healthy subjects.

24. Information relating to the dosage of 40 mg Lescol XL capsules b.i.d. should be ——— the Elimination section table in the labeling. Additionally, comparative information for the 40 mg b.i.d. dosage should be ——— the Clinical Studies section of the labeling. Finally, the Dosage and Administration section should have information for 40 mg capsule b.i.d. dosing ———

The reasoning for this is that some patients may respond better from toxicity or efficacy standpoints on the 40 mg capsule b.i.d. regimen than with the 80 mg XL Q day regimen, and therefore the 40 mg capsule b.i.d. regimen should be a treatment option. This is reasonable, especially since the 40 mg capsule will be available and is currently used under the labeling for both Qday and b.i.d. dosing.

Additionally, ——— would limit generic drug labeleling for that regimen, and would be an unnessary barrier to generic use of the drug.

QUESTION BASED REVIEW

1. What is the product, its pharmacologic class, and what is the proposed dosing regimen?

Lescol XL 80 mg. Tablets ('——— tablet) is a modified release formulation of fluvastatin, a HMG-CoA reductase inhibitor. The proposed labeling for this product is for one 80 mg tablet to be taken in the evening .

2. Are there other formulations of Lescol approved and what is their dosing regimen?

Fluvastatin Immediate release capsules are currently approved in the United States in strengths of 20 and 40 mg. The recommended starting dose for the majority of patients is 40 mg. The recommended dosing range is 40-80 mg/day. The daily regimen of 80 mg is given as 40 mg bid.

3. What information was submitted in support for the approval of Lescol XL?

Six controlled clinical studies have been submitted as well as four human Pharmacokinetic/Biopharmaceutic studies and CMC information. The clinical studies utilized the to be marketed formulation and there is no bioequivalence issue. The sponsor indicates that HFD-510 had agreed that no additional preclinical information beyond that which was submitted for NDA 20-261 (Lescol Capsules) would be required. Approval will be based on the submitted safety/efficacy trials.

4. What is the indication for Lescol XL?

Hypercholesterolemia and Dyslipidemia

It is indicated in hypercholesterolemia and dyslipidemia as an adjunct to diet to reduce elevated total cholesterol (Total-C), LDL-C, and TG, and to increase HDL-C in patients whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

Atherosclerosis

It is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

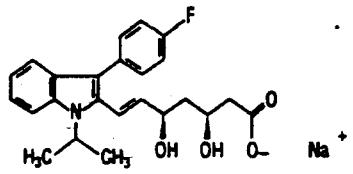
5. What is the mechanism of action of Fluvastatin?

Fluvastatin is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion

of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. Fluvastatin has two optical enantiomers, an active form, SDZ 62-735 and an inactive enantiomer SDZ 62-850. 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 end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

6. What are the physicochemical properties of fluvastatin?

Fluvastatin sodium is [*R**,*S**-(*E*)] -(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*--indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO4 \cdot Na$, its molecular weight is 433.46 and its structural formula is:



$C_{24}H_{25}FNO_4 \cdot Na$ Mol. wt. 433.46

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol.

7. What is the formulation of Lescol XL 80 mg Tablets?

Formulation of the to be marketed 8 h matrix tablet- Manufactured at Novartis, Stein, Switzerland

Composition of Lescol XL 80 mg hydrophilic matrix tablet formulations (mg/tablet)

	Formulation no.
Ingredient (Ph. Eur. / NF, USP)	
Tablet core	
Fluvastatin sodium[1]	
Microcrystalline cellulose fine	
Hydroxypropyl methyl cellulose	
Hydroxypropyl methyl cellulose	
/ Hydroxypropyl methyl cellulose	
Hydroxypropyl cellulose	

Potassium bicarbonate		
Povidone		
Magnesium stearate		
Core tablet weight		
Coating		
Total weight	334.75	334.75

8. What is known of PK/PD for the drug?

No PK/PD relationship has been established. However, elevated LFT's appear to be dose related, and efficacy in some patients may be increased with upward titration. The major adverse event which has been seen with this drug, as well as others in the class, is rhabdomyolysis and possible resultant renal failure.

9. What are the pharmacokinetic/metabolic parameters associated with Lescol XL?

Mass Balance
From IR Submission

Radiolabeled (tritium labeled) studies showed that 93-98% of the oral fluvastatin dose was absorbed. Absolute bioavailability following oral administration was about 24% (extraction ratio of approximately 0.76). Approximately 85-92% of the oral dose (total radioactivity) was excreted in the feces while the urinary recovery was about 5% of the dose.

Metabolism
From IR Submission

Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5- and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%).

Distribution

From IR Submission

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 0.35 L/kg. The parent drug is targeted to the liver and no active metabolites are present systemically.

Elimination

From IR Submission

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug.

Absorption

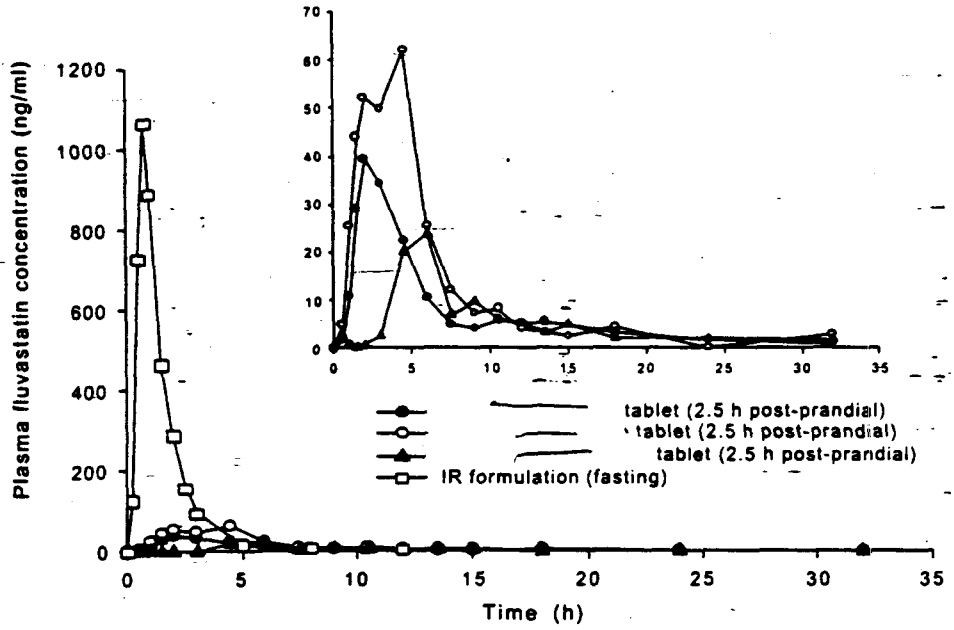
Study W251 Relative bioavailability of the fluvastatin 80 MR tablets under 2.5 h post-prandial and fed conditions

The mean relative bioavailability of the to be marketed XL tablet administered 2.5 hours after a lowfat AHA meal was approximately 29% (range: 9-66%) compared to that of the Lescol immediate release capsules administered under fasting conditions. The Cmax of the [redacted] to be marketed modified-release tablets administered 2.5 hours after the lowfat meal was only about 9% relative to the IR capsule (fasting). The median Tmax value was prolonged to about 3 hrs for the 8 hr matrix MR tablets administered 2.5 hours after the lowfat meal while the Tmax for the IR tablets administered under fasting conditions was 0.8 hr.

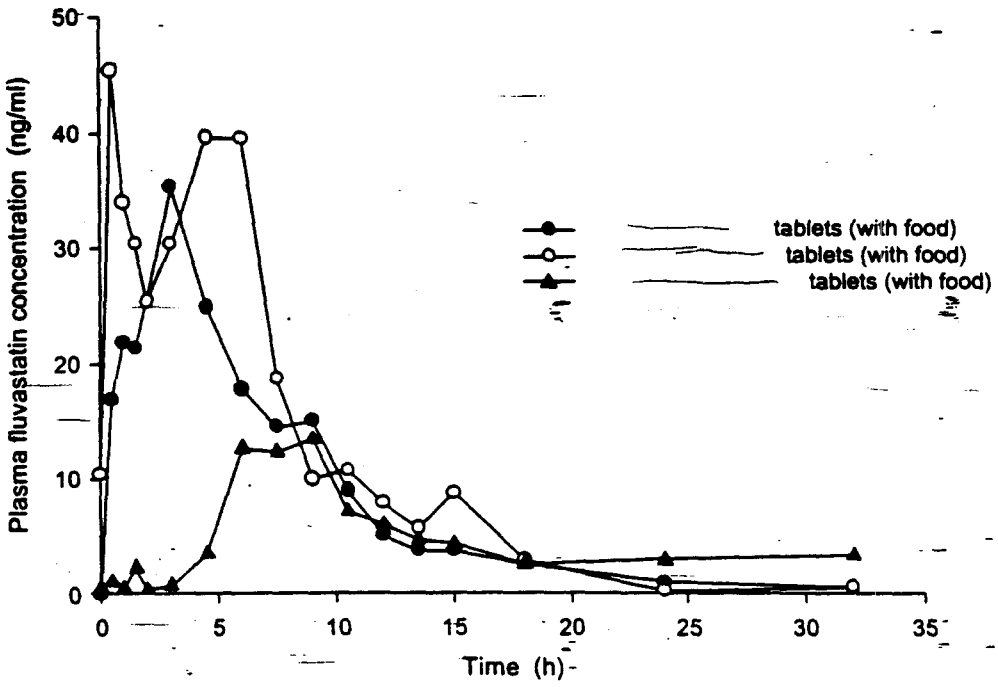
Mean ± SD of the pharmacokinetic parameters for Lescol XL under fed or 2.5 h post-prandial conditions and the IR Capsules under fasting conditions

Parameter	IR formulation 80 mg (2x40 mg) capsules (n=16) Fasted	[redacted] 80 mg tablets (n=16) Fed	MR [redacted] 80 mg tablets (n=16) 2.5 h post prandial
AUC t (ng.h/ml)	1453 ± [redacted]777	345 ± [redacted]260	361 ± [redacted]194
Cmax (ng/ml)	1104 ± [redacted]735	102 ± [redacted]72	98 ± [redacted]37
Tmax (h)	0.81 ± [redacted]0.3	2.9 ± [redacted]3.74	2.9 ± [redacted]1.4
Cmax/AUC t (1/h)	0.73 ± [redacted]0.22	0.334 ± [redacted]0.123	0.30 ± [redacted]0.09
MRT (h)	1.5 ± [redacted]0.3	5.31 ± [redacted]2.45	5.4 ± [redacted]2.6

Mean plasma fluvastatin concentration-time profiles in post-prandial (MR formulations) or fasted condition (IR formulation). (Insert : For MR formulations only)



Mean plasma fluvastatin concentration-time profiles in FED condition (MR formulations)



As shown in the table of ratios of fed vs 2.5 post prandial results below (low fat AHA meals used), the timing of a low fat meal relative to dosing did not appear to have a significant effect on the bioavailability of the to be marketed —— tablets. The ratios of AUCt, Cmax, and Tmax for the —— tablets in the fed state relative to the 2.5 hr post prandial state were all about 1.0.

Mean ratios of the pharmacokinetic parameters for —MR formulation fed vs 2.5 h post prandial (AHA meals)

Parameter	Ratio- —— Fed vs 2.5 h post prandial
AUC t (ng.h/ml)	0.96
Cmax (ng/ml)	1.04
Tmax (h)	1.0
Cmax/AUC t (1/h)	1.11
MRT (h)	0.98

Conclusions- Study W251

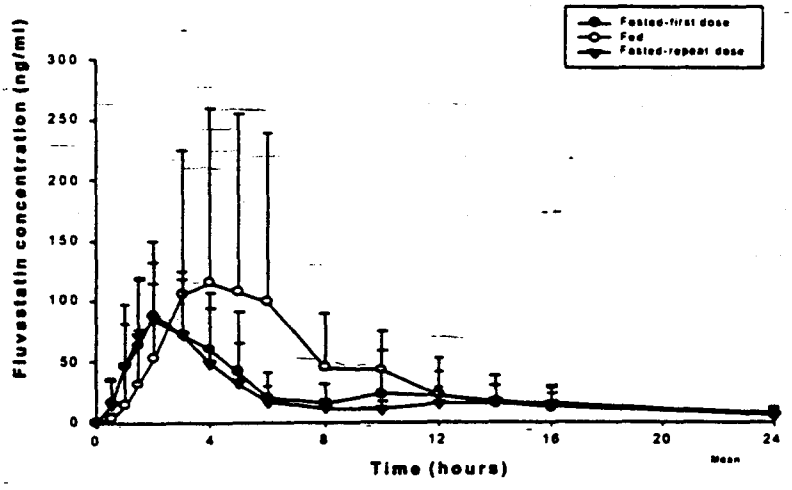
- The —— to be marketed modified release formulation resulted in a slower absorption and lower systemic availability and peak concentrations under fed and 2.5 h post prandial conditions (lowfat meals used) as compared to the marketed immediate release capsule under fasted conditions
- The to be marketed —— 80 mg tablet, dosed with a lowfat AHA meal had little affect on the AUC t , Cmax, or Tmax as compared to dosing the product 2.5 h after the meal
- The lower systemic availability and peak concentrations of the —— 80 mg tablet as compared to the IR capsules could reflect a longer and more sustained exposure of fluvastatin to the liver (increased hepatic extraction efficiency) without saturating the first-pass metabolism

Absorption

Study W351- Relative bioavailability of the to be marketed fluvastatin 8 hr 80 mg MR tablets under fasted and high fat meal conditions

Administration of a high fat meal delayed the absorption (Tmax: 6 h vs 2 hr) and increased the bioavailability of the XL tablet by approximately 50% relative to fasting. Once Fluvastatin XL begins to be absorbed, fluvastatin concentrations rise rapidly (See Appendix I- Individual subject concentration vs time profiles- Study W351). Overall variability in the pharmacokinetics of Lescol XL is large (42-64% CV for Cmax and AUC), and especially so after a high fat meal (63-89% for Cmax and AUC). Intrasubject variability in the pharmacokinetics of Lescol XL under fasting conditions (about 25% for Cmax and AUC) tends to be much smaller as compared to the overall variability. Multiple peaks in plasma fluvastatin concentrations have been observed after to be marketed —— Lescol XL administration.

Mean±SD serum fluvastatin concentration-time profiles following a single oral dose of 80 mg MR formulation:



The mean pharmacokinetic parameters of fluvastatin with & without food are listed below:

Mean ± SD pharmacokinetic parameters of fluvastatin following a single 80 mg dose of to be marketed 80 mg MR tablet-*(N=24 unless otherwise specified)*

Parameter	Fasted - first dose	Fed	Fasted - Repeated dose	90% CI
C_{max} (ng/ml)	126.2 ± 53.3	183.1 ± 163.4	107.2 ± 45.3	0.86-1.51
C_{max} Ratio*	-	1.63 ± 1.27	0.94 ± 0.35	
Median t_{max} (h)	2	6	2	p<0.01
AUCt(h.ng/ml)	578.3 ± 340.9	858.5 ± 632.6	503.4 ± 246.3	1.09-1.78
$AUC_{(0-24)}$ (h.ng/ml)	579.0 ± 340.9	861.1 ± 632.3	505.7 ± 245.5	1.09-1.79
AUC_{24} Ratio*	-	1.74 ± 1.11	0.94 ± 0.28	
AUC∞ (h.ng/ml)	692.8 ± 441.8 (N=14)	1060.0 ± 669.7 (N=17)	611.7 ± 280.5 (N=13)	0.93-1.66
C_{max}/AUC24	0.24 ± 0.07	0.20 ± 0.06	0.22 ± 0.06	
T1/2 (h)	7.0 ± 3.8 (N=14)	4.3 ± 3.2 (N=17)	5.5 ± 2.9 (N=13)	

*Ratios: Mean of ratios relative to the first dose under fasted condition.

Conclusions- Study W351:

- Food increases the systemic availability (C_{max} and AUC) by about 50% for fluvastatin from the 80 mg —— tablet formulation. In some subjects, the increase in availability and Cmax is substantially greater. The medical reviewing division has indicated that this degree of food effect on absorption should not have any impact on safety or efficacy, and that the sponsor should be allowed to indicate in the labeling that the product can be taken without regard to food.
- After absorption begins, fluvastatin concentrations rise rapidly from the —— tablets fluvastatin. under fed and fasted conditions. This may be due to either relatively rapid release, concentration dependent nonlinear kinetics, or a combination of both
- The apparent terminal half-life of the —— is approximately 2-3 fold longer than that observed for the IR capsule (5 to 7 hours vs. 2.7 hours, respectively)
- The intrasubject variability for the C_{max} and AUC parameters was estimated to be approximately 25%. This was less than the intersubject variability (CV) of approximately 42-64% without food, and 63-89% with food. From this data, it appears that the systemic availability of fluvastatin from the —— tablet is highly variable, and especially so with food

- The medical reviewing division has indicated that the differences seen as a result of the effects of food will not result in clinically important differences in safety or efficacy, and that the sponsor should be able to keep its labeling that indicates that Lescol XL may be taken without regard to food.

10. Has a dose proportionality study been performed for the Lescol XL tablets?

Neither a single dose nor multiple dose, dose proportionality study has been performed on the to be marketed — 80 mg — Lescol XL tablet. No such study is required as only one dose will be approved for the product (1 x 80 mg tablet in the evening).

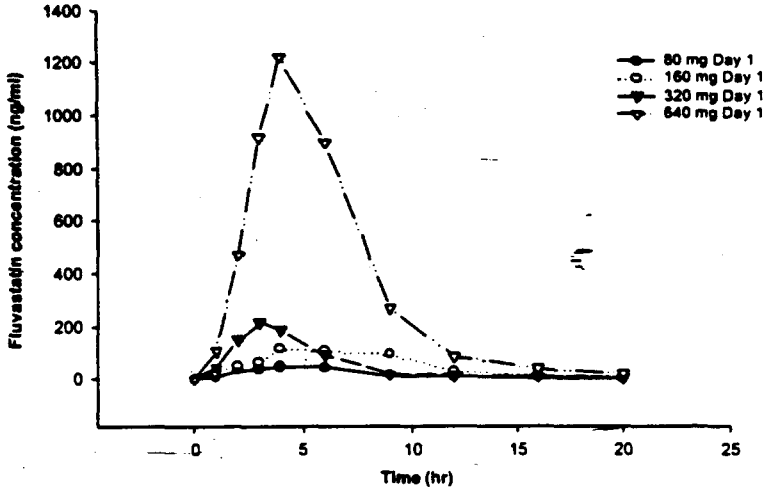
11. Has a bioavailability study comparing the 80 mg to be marketed XL tablet dosed Q day (sponsor's proposed regimen) to the approved 40 mg b.i.d. capsule regimen been as is called for in CFR 320.25(f)?

Such a study has not been conducted. A steady state dose proportionality study covering single daily doses ranging from 80 to 640 mg of a slower releasing (———— tablet has been conducted (Study W253). This study showed accumulation beyond expected for dosing greater than the 80 mg level. The study demonstrated single dose non-dose proportionality beyond 320 mg doses, and steady state non-dose proportionality between the 80 and 640 mg dosage levels.

Mean ± SD pharmacokinetic parameters of fluvastatin following a single 80-640 mg dose —— formulation (Day 1).

Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	61 ± 16	162 ± 46	274 ± 134	1388 ±919
Median Tmax (h)	4	4	3.4	4
AUCt (h.ng/ml)	334 ± 124	976 ± 321	1013 ± 489	6854 ± 5333
AUC∞ (h.ng/ml)	349 ± 133	1029 ± 337	1055 ±502	6966 ± 5387
CL/f (ml/hr)	266 ± 119	169 ± 50	388 ± 209	123 ±75
T1/2 (h)	4.5 ± 1.8	4.9±3.1	5.1±2.8	3.6±0.5

Mean serum fluvastatin concentration-time profiles following a single oral dose of 80 - 640 mg ——— formulation (Day 1).

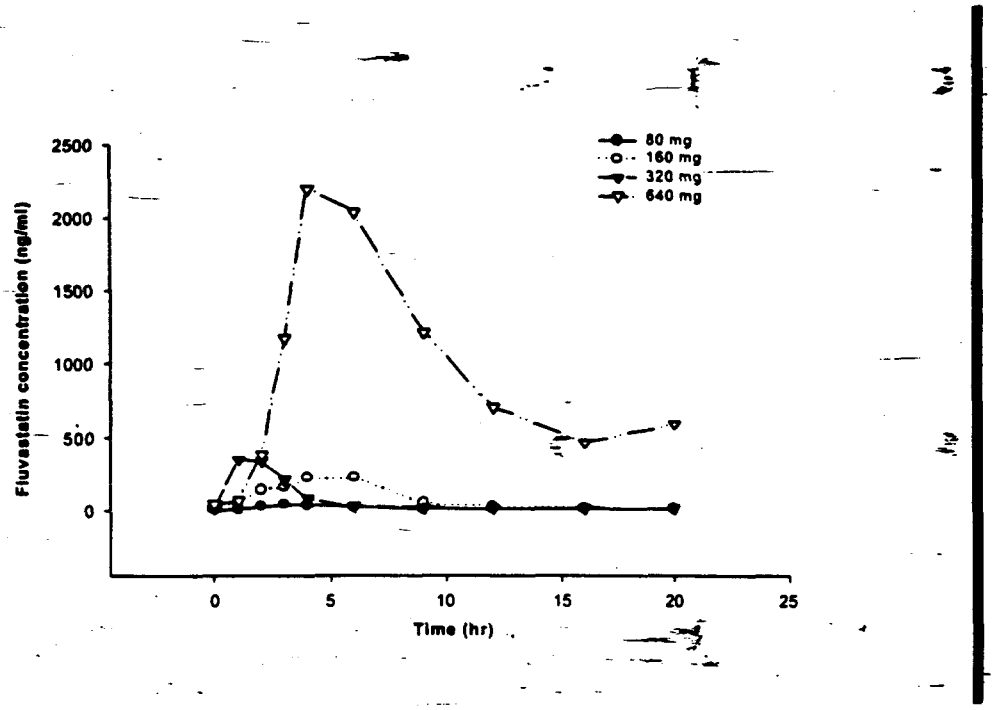


The steady state pharmacokinetic results are presented in the table and figure below:

Mean ± SD pharmacokinetic parameters of fluvastatin following a once-a-day 80-640 mg ——— formulation for 13 days (Day 14)

Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	55 ± 27	331 ± 100	586 ± 239	4917 ± 3393
Median Tmax (h)	3	4	4	4
Cmin (ng/ml)	2.8 ± 3.3	7.3 ± 3.6	10.1 ± 7.4	80.7 ± 91.5
AUCt (h.ng/ml)	282 ± 124	1562 ± 486	2744 ± 1645	32189 ± 29339
AUC∞ (h.ng/ml)	361 ± 141 (N=5)	1609 ± 497	2961 ± 1592	42993 ± 40290
CL/f (ml/hr)	345 ± 174	116 ± 54	170 ± 132	39 ± 34
T1/2 (h)	4.7 ± 1.9 (N=3)	3.5 ± 0.9	8.9 ± 12.5	5.4 ± 4.4
Fluctuation Index	4.5 ± 1.2	5.2 ± 1.4	5.5 ± 1.1	4.3 ± 1.4
Acc. Factor	0.91 ± 0.4	2.1 ± 0.6	3.0 ± 2.6	4.9 ± 3.1

Mean serum fluvastatin concentration-time profiles after once-a-day oral dosing of 80 - 640-mg ——— formulation for 13 days (Day 14).



As seen in the table below, nonlinearity in the pharmacokinetics above single doses of 320 mg for the ——— tablet is very evident with a 640 mg dose producing a mean value for AUC 0-00 of 2.5 times of that expected under linear conditions based on the 80 mg dose of the ——— tablet :

Mean dose normalized (value x 80mg/dose) pharmacokinetic parameters of fluvastatin following a single 80-640 mg dose ——— formulation (Day 1).

Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	61	81	69	174
AUCt (h.ng/ml)	334	488	253	857
AUC∞ (h.ng/ml)	349	514	264	870
AUCoo Beyond Expected if linear Dose Normalized AUC t /AUC t 80mg	1	1.5	0.8	2.5

As seen in the table below, under steady state conditions, nonlinearity was evident beyond the 80 mg dosage level for the ——— tablet. Mean values of AUCt ss of 2.8, 2.4, and 14.3 times those expected under linear steady state conditions (based on the 80 mg dose) were seen at the 160, 320, and 640 mg dosage levels.

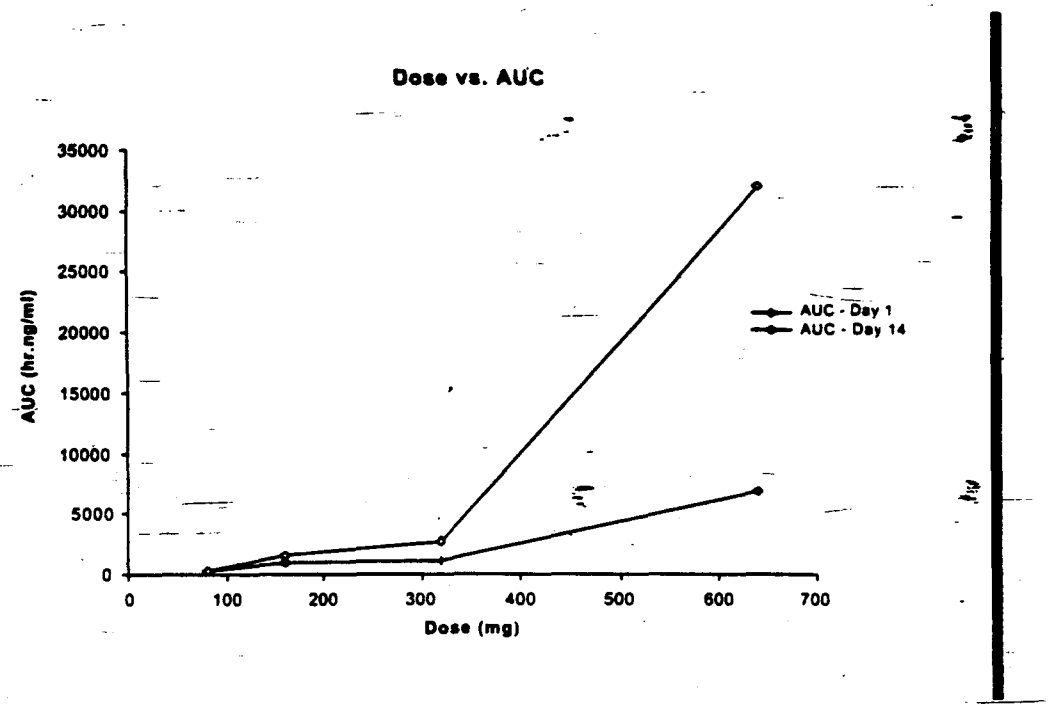
Also as seen in the table below, going from single dose to steady state, nonlinearity was evident beyond the 80 mg dosage level for the ——— tablets, producing mean accumulation values for AUCt ss/AUCoo sd of 1.5, 2.6, and 4.6 times of those expected under linear single dose to steady state conditions for the 160 , 320, and 640 mg dosage levels.

Mean dose normalized (value x 80mg/dose) pharmacokinetic parameters of fluvastatin following a once-a-day 80-640 mg ——— formulation for 13 days (Day 14)

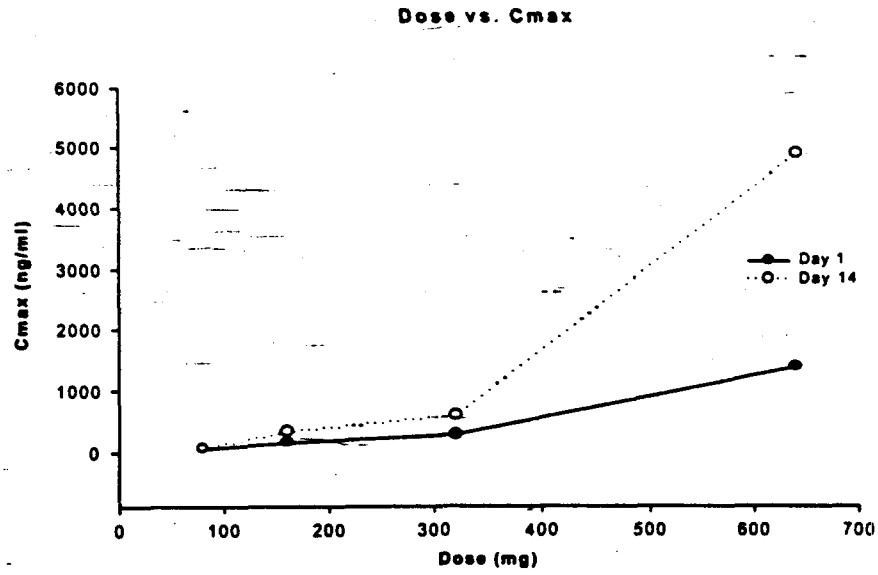
Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	55	166	147	615
Cmin (ng/ml)	2.8	3.7	2.5	10
AUCt (h.ng/ml)	282	781	686	4024
AUC∞ (h.ng/ml)	361	805	740	5374
AUCt ss Beyond Expected if linear-Multiple Dose Dose Normalized AUCt ss/AUCt ss 80 mg	1	2.8	2.4	14.3
Accumulation Beyond Expected if linear Single Dose to Multiple Dose AUC t ss/AUC oo sd	0.8	1.5	2.6	4.6

The figures below graphically demonstrate the departure from linearity in AUC and Cmax under single dose and steady state conditions over the 80 to 640 mg dosage range for the ——— tablet:

Dose vs mean AUC following a single and multiple doses of 80-640 mg MR formulation.



Dose vs mean Cmax following a single and multiple doses of 80-640 mg MR formulation.



Conclusion- Study W253

- Fluvastatin dosed using the [redacted] tablets possesses both dose and time dependent nonlinear pharmacokinetics
- Fluvastatin dosed using the [redacted] tablets is not dose proportional under single dose conditions beyond 320 mg, and multiple dose conditions beyond 80 mg.
- Fluvastatin multiple dosing using the [redacted] tablets shows accumulation beyond expected at the dosage levels beyond 80 mg single daily doses (1.5, 2.6, and 4.6 times beyond expected for the 160, 320, and 640 mg dosage levels)
- Although the formulation used in this study is a slower releasing one than the to be marketed one, it is conservatively predictive of the situation with the more rapidly releasing to be marketed [redacted] tablet. Greater non-dose proportionality and accumulation beyond expected would be predicted for the more rapidly releasing to be marketed [redacted] tablet due to its potential of greater saturation of the first pass metabolic process.
- Since only one dose and strength of the to be marketed 80 mg [redacted] tablet will be approved , there is no dose proportionality issue, however, there are issues regarding steady state accumulation and steady state comparative (to a reference) bioavailability as no study to examine these issues was conducted. It is being recommended that such a study be performed on a phase IV basis to address these issues and fulfill the regulatory requirements for controlled release products under CFR 320.25(f), provided there is adequate safety information to support the use of 80 mg daily doses of the Lescol XL tablet.

12. Were the analytical methods as specifically utilized to characterize plasma fluvastatin concentrations in the submitted in vivo studies acceptable?

[redacted] methods were used to characterize the plasma fluvastatin concentrations. The assays performed acceptably for the reviewed in vivo studies in terms of reproducibility, accuracy, specificity, and sensitivity. The fluvastatin concentration range covered by the assays ranged from [redacted] and LLOQ was [redacted]

13. Have the pharmacokinetic claims for the to be marketed 80 mg Lescol XL tablet been adequately supported?

Specifically, the labeling statement which claims the product is [redacted] has not been demonstrated by the sponsor, and it has been recommended that this wording be removed from the labeling. Looking at the individual subject concentration vs time profiles from the high fat meal vs fasting study (W351) in Appendix I, it can be seen that in general, concentrations do not increase gradually, but increase rather abruptly. This is especially true for the fed treatment. It is difficult to access whether this is due to rapid release, concentration dependent nonlinearity, or a combination of

both. To better assess the issue of the rate of absorption, deconvolution assessments should have been conducted as called for in the Controlled Release Guideline (1984).

14. Have drug interactions been addressed?

No new information has been presented beyond that already presented in the current labeling for the approved immediate release fluvastatin capsules. As this labeling may not be completely relevant to the Lescol XL tablet due to different bioavailability and pharmacokinetics as compared to the IR product, certain labeling modifications have been proposed for the **Drug Interaction** section of the labeling (See 17. What labeling modifications to the proposed labeling were recommended?).

15. Have differences in special populations been addressed for Lescol XL?

The only new special population information presented for Lescol XL is that for gender.

Gender

In study W351 (Single 80 mg Lescol XL doses, repeat measures, high fat food vs fasting study) there were 12 male and 12 female subjects. The mean value for C_{max} in female subjects was approximately 45% greater than those seen in male subjects in both the fed and fasted states. The mean value for AUC in female subjects was approximately 67% and 77% greater than those seen in male subjects in the fed and fasted states. The extent of variability was high in both groups, similar to that observed in the overall data.

Mean ± SD Pharmacokinetic parameters of fluvastatin in male and female subjects following an 80 mg tablet dose

Parameter	Fasted		Fed	
	Male (N=12)	Female (N=12)	Male (N=12)	Female (N=12)
C_{max} (ng/ml)	103.1 ± 37	149.3 ± 59	149.7 ± 121	216.4 ± 197.1
AUC24 (h.ng/ml)	418.6 ± 163	739.3 ± 399	644.2 ± 336	1077.9 ± 788

Conclusions- Gender- Study W351:

- Females have substantially greater bioavailability of Lescol XL as compared to males (about 45% greater for Cmax and 67-77% greater for AUC)

17. Have the necessary dissolution studies been conducted, and has an appropriate dissolution method and specification been proposed?

In Vitro Dissolution

The solubility profile of fluvastatin, Sodium is presented below:

Solubilities of the drug substance (Fluvastatin sodium) in aqueous solvents at 37° C

Solvent	mg Fluvastatin Na / ml solvent	Parts Solvent / Parts Solute	Solubility
pH 1.1 Hydrochloric acid	0.076	13158	Insoluble
pH 4.0 Acetate buffer	0.158	6329	Very Slightly Soluble
pH 6.1 Phosphate buffer	1.97	507	Slightly Soluble
pH 7.8 Phosphate buffer	101.0	10	Freely Soluble
pH 9.0 Water, no buffer	169.0	6	Freely Soluble

Fluvastatin sodium is very water soluble, and the current method for the marketed capsules uses [redacted] as the dissolution medium. Although [redacted] could also be used for the modified release tablets, the medium was initially changed to [redacted] since this was more physiologically relevant. [redacted] was chosen since this is typically used for tablets. Drug release was also tested using [redacted] but the rate was markedly slower due to lower solubility at [redacted] Dissolution media at [redacted] was not tested since fluvastatin is almost insoluble at those pHs.

Due to two problems associated with the use of [redacted] was used. Using [redacted] as the medium and [redacted] resulted in much less tablet-to-tablet variability than that with [redacted]

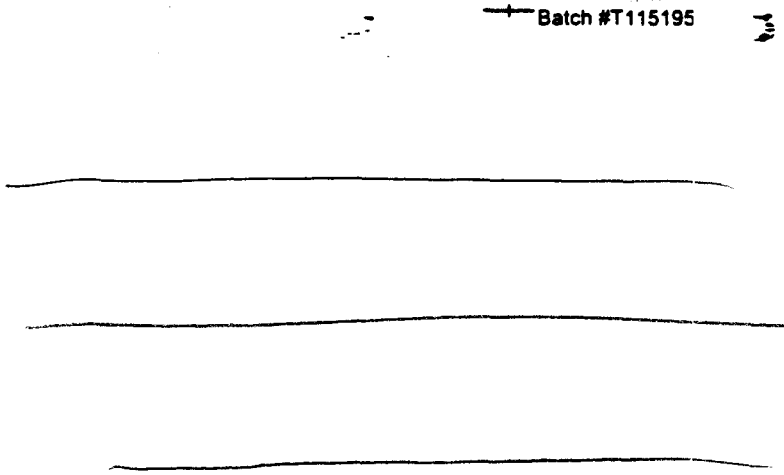
The sponsor reports that in vivo data suggested a relatively fast release rate of drug substance from the [redacted] tablet, faster than the in vitro data in [redacted] indicated. After an in vitro study evaluating [redacted] and [redacted] with varying [redacted] was selected as the medium since it more closely fit the suggested fast release in vivo.

In vitro dissolution profiles of the [redacted] based 80-mg fluvastatin MR tablet have been characterized in different dissolution media. The profiles were obtained up to [redacted] using [redacted] of each medium. The media included [redacted] The dissolution profiles are presented below. The dissolution profiles showed that the amount of release was the lowest in the [redacted] whereas the released amount was maximized in [redacted] and the percent dissolved was [redacted] Various strengths of [redacted] showed different degrees of dissolution amounts. Among the [redacted] as the [redacted] dissolution decreased suggesting, in part, an [redacted] on fluvastatin dissolution profile.

Comparative dissolution of Lescol XL 80 mg tablets, batch H-05018

(Batch used in study W251)

Dissolution profile of Lescol XL 80 mg tablet, batch T115195
(Batch used in study W351)



On average the dissolution in showed about release in 2 h, about release in 4 h and dissolution in about 8 hours. Similar dissolution profiles were observed in for two different batches. Batch no. H-05018 (clinical trial lot) was tested using whereas Batch no. T 115195 (Study W351) was tested using Both methods used Although these observations suggest that as a medium could be a suitable method for testing dissolution of fluvastatin 80 mg MR tablets, was selected for the reasons mentioned earlier.

Individual and mean dissolution data generated using the proposed method and conditions were provided for batches T115195, T116008, T116009, D-01-98, H-05286, H-05287, and H-05290 in a March 1, 2000 submission at the request of OCPB, and mean and range dissolution data for lot H05018 in a September 28, 2000 submission.. This information is contained in Appendix III.

Data for lot H-05018 used in bioavailability study W251 appears below:

Table 2. Dissolution data for Lescol XL Tablets, 80 mg, batch no. H-05018, using method version C

	Cumulative percent release[1]			
Tablet no.	0.5 hrs.	2 hrs.	4 hrs.	8 hrs.
1				
2				
3				
4				
5				
6				
Average	6.6	26.3	60.1	102.7
RSD (%)	7.4	3.8	4.9	1.3

[1]Data from 24 month stability at 25°C/60%RH stored in a

Data for lot T115195 which was in bioavailability study W351 appears below:

Lescol XL film-coated tablets, 80 mg
Analytical development and justification of specifications JS6012/A

Table 2. Comparison of dissolution data

			Dissolution, average [min, max]			
Batch	Apparatus	rpm	0.5 hours	2 hours	4 hours	8 hours
T115195[1]			7 [ ]	29 [ ]	60 [ ]	96 [ ]
	% RSD		17.9	22.4	18.5	3.7
			6 [ ]	26 [ ]	60 [ ]	100 [ ]
	% RSD		11.8	11.2	9.7	0.9

The sponsor reports that the four time points given below were chosen for the specification using The time points evaluate dose dumping and a release of approximately one-third, two-thirds and complete release of the drug substance.

Proposed dissolution limits for fluvastatin sodium MR tablet

Time	Drug released
0.5 hours	
2 hours	
4 hours	
8 hours	

It is reported that the limits were determined by evaluation of dissolution data obtained from in vivo batches, registration stability batches and production batches at time of release and from stability data on these batches. It is reported that based upon these limits, five samples would have gone to Stage 2 testing.

Conclusion – Dissolution

OCPB recommended dissolution limits for fluvastatin sodium MR tablet

Time	Drug released
0.5 hours	
2 hours	
4 hours	
8 hours	

OCPB recommends that dissolution specifications be set based on the lots that were used in the bioavailability studies. These lots were also of the same formulation of those used in the clinical studies. Based on this rationale, the 2 and 4 hour sponsor proposed specification s are excessively wide and OCPB recommends a 2 hour specification of and a specification of OCPB agrees with the 0.5 and 8 hour specifications of

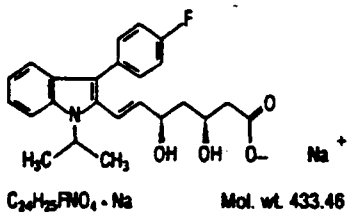
16. What labeling modifications to the proposed labeling were recommended?

The comparative labeling between the sponsor's proposed labeling and OCPB's recommended modified labeling is presented below. Changed material by OCPB is in highlighted, with new material being highlighted and underlined and sponsor text which OCPB recommended for removal being highlighted and "struck-out.". All of these OCPB changes have been agreed to by the sponsor and the medical reviewing division. The OCPB changes appear in the Clinical Pharmacology, Precautions, and Dosage and Administration sections of the labeling.

21 pages redacted from this section of the approval package consisted of draft labeling

BACKGROUND

Fluvastatin sodium is [*R**,*S**-(*E*)] -(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*--indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO4 \cdot Na$, its molecular weight is 433.46 and its structural formula is:



$C_{24}H_{25}FNO_4 \cdot Na$ Mol. wt. 433.46

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium (Lescol®, SDZ XUO 320) is a potent synthetic competitive inhibitor of hydroxymethylglutaryl-CoA reductase (HMGR), the enzyme responsible for converting 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor for cholesterol. Thus fluvastatin limits cholesterol biosynthesis. 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 end result of this biochemical process is a reduction of blood cholesterol.

Lescol® is approved and marketed in the U.S. and several other countries in Europe for the treatment of hypercholesterolemia, mixed dyslipidemia and slowing the progression of coronary atherosclerosis (more than 20 countries).

Fluvastatin undergoes first pass metabolism, which begins to show non-linear kinetics (competitive inhibition) at doses higher than 20 mg and result in higher than expected systemic concentrations at higher doses. Although fluvastatin undergoes extensive metabolism, only the parent drug, fluvastatin, is the active moiety and its metabolites are not considered to be active. Fluvastatin has a short elimination half-life (1.5-2 h); therefore, accumulation of fluvastatin is unlikely after chronic dosing with the IR product.

Currently, the approved dose of Lescol® is 20-80 mg per day. Usually, doses at or below 40 mg are taken once a day at bedtime. Doses of 80 mg are to be taken in divided doses (40- mg twice a day). Although Lescol has been well tolerated, some adverse events (AEs) such as elevation in transaminase levels, headache, and dyspepsia have been reported..

The sponsor indicates that in order to increase the tolerability and reduce the occurrences of AEs, a modified release (MR) formulation of fluvastatin has been developed. The MR formulation delivers fluvastatin at a slower rate than the conventional immediate release (IR) capsule; thus reducing first pass saturation resulting in lower systemic exposure. The sponsor states that this, in turn, should allow for a higher dose with increased efficacy and tolerability of fluvastatin. An 80- mg ——— MR tablet was developed and studied for its safety and efficacy in hyperlipedimic patients. Additionally, the 80- mg MR tablet was studied in humans for its pharmacokinetic characterization.

A total of four studies were conducted in humans to characterize the pharmacokinetics of fluvastatin MR (Lescol XL) tablets and the results of these studies are presented below. Pivotal safety and efficacy trials for the matrix based 80 mg MR tablet were conducted using the final market formulation. Therefore, a bioequivalence study was not necessary for the 80 mg Lescol XL.

Study W251
Relative bioavailability of the fluvastatin 80 MR tablets under 2.5 h post-prandial and fed conditions

Project: SDZ XUO 320

Title of study: A two-phase, seven-period, open-label, randomized, crossover study to evaluate three 80 mg, modified-release, SDZ XUO 320 tablets differing by formulation method and release rate.

Investigator(s)

Study period: first subject dosed 18-Feb-97 last subject completed 07-Mar-97

Primary Objective: To compare the pharmacokinetic profiles of three tablet formulations of SDZ XUO 320 after oral administration under fed and 2.5 hour postprandial conditions in healthy subjects.

Secondary Objective: To compare the pharmacokinetic profiles of Lescol® capsules under fasting conditions and three tablet formulations of SDZ XUO 320 under the 2.5 hour postprandial condition in healthy subjects.

The relative bioavailability of two different 80 mg MR tablets, , and one 80 mg tablet were determined as compared to two 40 mg marketed immediate release (IR) Lescol® capsules in this crossover study (dose: 80 mg). Additionally, pharmacokinetic comparisons were also made among the 80 mg MR and tablets under fed condition.

This was a two phase, seven period, open-label, randomized crossover study. A total of sixteen healthy volunteers (male and female) completed this study. In the first four periods (Phase I), volunteers received fluvastatin 80 mg MR tablets in the morning under either 2.5 h post-prandial or fed (Standard American Heart Association Meal- 800 calorie breakfast) conditions as per the randomization schedule. In period 5 (Phase I), all volunteers received two-40 mg IR fluvastatin capsules under fasted condition in the morning. In periods 6 and 7 (Phase II), all volunteers received 80 mg , formulation under either 2.5 h post-prandial or fed conditions in the morning.

The timing of sample collection was as follows:

Fluvastatin pharmacokinetic serum samples (modified release formulations): morning pre-dose, 0.50, 1, 1.5, 2, 3, 4.5, 6, 7.5, 9, 10.5, 12, 13.5, 15, 18, 24 and 32 hours post dose

Fluvastatin pharmacokinetic serum samples (immediate release capsules): morning pre-dose, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 5, 8, and hours post dose

Products Used in Study

SDZ XUO 320 80 mg slow release tablets ( )FCN #: 3745999.00.002.B Batch # H-05020

SDZ XUO 320 80 mg slow release tablets ,FCN #: 3745999.00.003.C Batch # H-05018

SDZ XUO 320 80 mg slow release tablets FCN #: 3745999.00.001.A Batch # H-05017

Lescol® 40 mg capsules (commercially available)

Formulation of the tablets- Manufactured in East Hanover, NJ

Composition of Lescol XL 80 mg tablet formulations (mg/tablet)

Ingredient (Ph. Eur. / NF, USP)	Formulation no. 2	3
Tablet core		
Fluvastatin sodium[1]		
Microcrystalline cellulose		
Hydroxypropyl cellulose		
Potassium bicarbonate		
Povidone		
Magnesium stearate		
Core tablet weight		
Coating		
Total weight	334.75	334.75

[1] of the sodium salt of Fluvastatin is equivalent to of Fluvastatin free acid

[2] Lescol XL 80 mg tablet /

[3] Lescol XL 80 mg . tablet The formulations are identical. The change in the Novartis reference no. reflects a minor change in the manufacturing process.

[4] Removed during processing

Analytical Section

Serum concentrations of fluvastatin were determined by a [redacted]. For the study samples, all unknown concentrations were calculated from a calibration curve generated from extracted serum standards prepared for each assay run.

An 8-point calibration curve was produced with each analysis run, using serum calibration standards for fluvastatin over the range of [redacted]. Three serum Quality Control (QC) sample concentrations were also prepared prior to sample analysis and assayed in duplicate on each analysis day.

Summary results for the back-calculated standard concentrations from the 58 calibration runs are summarized below:

Summary of fluvastatin calibration parameters and back-calculated concentrations

Calibration Parameters (n = 58)								
Parameter	Mean	Range				%CV		
Correlation Coefficient (r)	0.9993	[redacted]				0.12		
Theoretical and Observed Back-Calculated Plasma Concentrations (ng/ml)								
	2	5	10	50	250	500	800	1000
Mean	[redacted]							
%CV	[redacted]							

Results from the analysis of frozen plasma QC samples containing fluvastatin at concentrations of 6, 200 and 750 ng/ml are shown below:

Summary of fluvastatin quality control (qc) sample analyses

QC Sample Nominal Concentration (ng/ml)	Number of Analyses	Mean Observed Concentration (ng/ml)	Range of Observed Concentrations	Interassay %CV
6.0	113	[redacted]	[redacted]	[redacted]
200	116	[redacted]	[redacted]	[redacted]
750	117	[redacted]	[redacted]	[redacted]

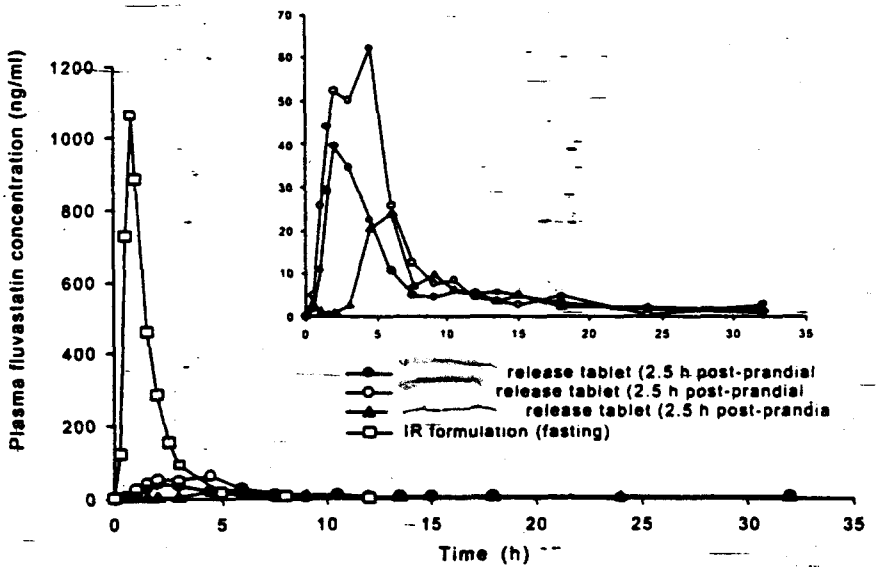
The accuracy of the assay was also assessed through the comparison of the mean observed concentrations to the nominal concentrations of fluvastatin in the prepared QC samples. The observed mean values were found to be within [redacted] of the nominal concentration for each of the three QC sample concentrations.

The analytical methodology and performance were acceptable for purposes of the study.

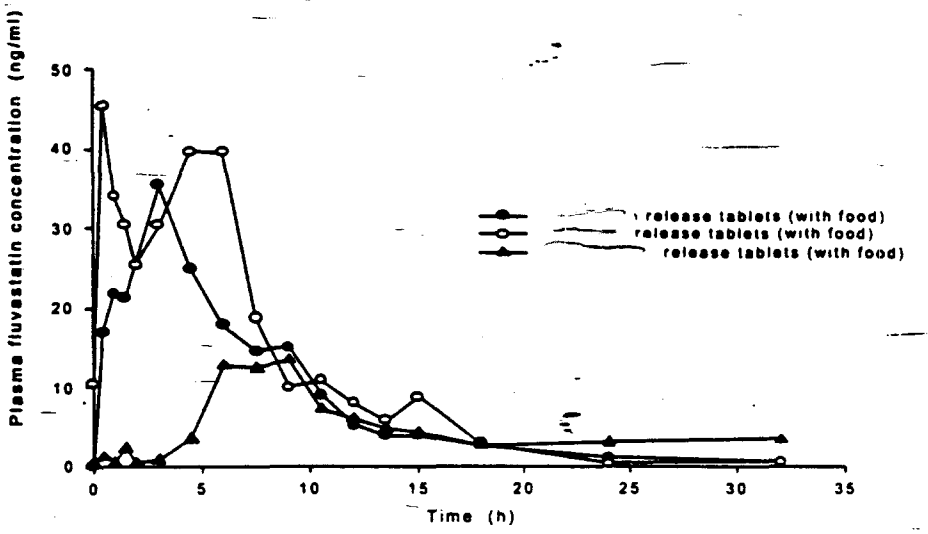
Results

The serum fluvastatin concentrations following 2 x 40 mg of the immediate release capsule were much higher than those observed with any of the 80 mg modified release formulations. The absorption from the MR formulations was more gradual as compared to the IR product. The mean serum fluvastatin concentrations over time are presented in the figures below.

Mean plasma fluvastatin concentration-time profiles in post-prandial (MR formulations) or fasted condition (IR formulation). (Insert : For MR formulations only)



Mean plasma fluvastatin concentration-time profiles in FED condition (MR formulations)



The study results showed that the ——— MR tablets were about 18% and 29% bioavailable under 2.5 h post-prandial condition relative to the IR capsule under fasted condition and the relative bioavailability of the ——— formulation was about 12% vs the IR product. The Cmax of the modified release formulations were also much less (4-9%) relative to the IR capsule. The median Tmax values were prolonged for the ~ MR tablets and the —— formulation relative to the IR tablet.

The pharmacokinetic data under the 2.5 post prandial condition showed that the AUC and Cmax of the ——— tablet were approximately 63 and 104% higher than that of the ——— tablet. On the other hand, the ——— formulation was approximately 50% less in AUC and about 47% less in Cmax. than the ——— MR tablet. Tmax was about 28% shorter for the ——— and about 197% greater for the —— formulation relative to the ——— tablet. The following table lists the pharmacokinetic parameters under the fed condition.

Mean ± SD of the pharmacokinetic parameters for Fluvastatin under the 2.5 h post-prandial (MR formulations) or fasting condition (IR formulation)

Parameter	IR formulation 80 mg (2x40 mg) capsules (n=16)	——— 80 mg tablets (n=16)	—— 80 mg tablets (n=16)	——— 80 mg tablets (n=13)
AUC t (ng.h/ml)	1453 ± 777	361 ± 194	221 ± 105	181 ± 171
Cmax (ng/ml)	1104 ± 735	98 ± 37	48 ± 22	52 ± 84
Tmax (h)	0.81 ± 0.3	2.9 ± 1.4	2.1 ± 0.9	8.6 ± 6.4

Cmax/AUC t (1/h)	0.73 ± 0.22	0.30 ± 0.09	0.23 ± 0.05	0.23 ± 0.17
MRT (h)	1.5 ± 0.3	5.4 ± 2.6	6.7 ± 1.9	10.3 ± 4.4

The pharmacokinetic data under the fed condition showed that the AUC and Cmax of the ——— tablet were approximately 35-40% higher than that of the ——— tablet. On the other hand, the ——— formulation was approximately 52% less in AUC and about 72% less in Cmax. than the ——— MR tablet. Tmax was slightly shorter for the ——— and about 3 times longer for the ——— ormulation relative to the ——— tablet. The following table lists the pharmacokinetic parameters under the fed condition.

Mean ± SD of the pharmacokinetic parameters for fluvastatin under fed condition

Parameter	——— 80 mg tablets (n=16) Fed	——— 80 mg tablets (n=16)	——— 80 mg tablets (n=11)
AUC t (ng.h/ml)	345 ± 260	253 ± 140	167 ± 90
Cmax (ng/ml)	102 ± 72	72 ± 65	29 ± 21
Tmax (h)	2.9 ± 3.74	3.4 ± 2.70	9.6 ± 5.3
Cmax/AUC t (1/h)	0.334 ± 0.123	0.293 ± 0.124	0.167 ± 0.065
MRT (h)	5.31 ± 2.45	6.21 ± 2.81	13.35 ± 4.59

As shown in the table of ratios of fed vs 2.5 post prandial results below, food did not appear to have a significant effect on the bioavailability of the ——— tablets. The Cmax for the ——— tablets in the fed state were 1.04 and 1.50 times their values in the 2.5 h post prandial state.

Mean ratios of the pharmacokinetic parameters for MR formulations fed vs 2.5 h post prandial (AHA meal)

Parameter	Ratio- ——— Fed vs 2.5 h post prandial	Ratio- ——— Fed vs 2.5 h post prandial	Ratio- ——— Fed vs 2.5 h post prandial
AUC t (ng.h/ml)	0.96	1.14	0.92
Cmax (ng/ml)	1.04	1.50	0.56
Tmax (h)	1.0	1.62	1.16
Cmax/AUC t (1/h)	1.11	1.27	0.73
MRT (h)	0.98	0.93	1.30

As shown in the table below, the systemic availabilities for the ——— tablet under 2.5 h post prandial and fed conditions were 1.63 and 1.36 times the ——— tablets under the same conditions. The Cmaxs for the ——— tablet under fed conditions were 2.04 and 1.42 times the ——— tablets under the same conditions.

Mean ratios of the pharmacokinetic parameters for ——— MR formulation 2.5 h post prandial or fed (AHA meal) VS ——— MR formulation 2.5 h post prandial or fed (AHA meal)

Parameter	Ratio- ——— 2.5 h post prandial VS ——— 2.5 h post prandial	Ratio- ——— Fed VS ——— Fed
AUC t (ng.h/ml)	1.63	1.36
Cmax (ng/ml)	2.04	1.42
Tmax (h)	1.38	0.82
Cmax/AUC t (1/h)	1.30	1.14
MRT (h)	0.80	0.86

Conclusion

Overall results showed that all of the modified release formulations resulted in a slower absorption and lower systemic availability and peak concentrations under fed and 2.5 h post prandial conditions as compared to the marketed immediate release capsule under fasted conditions. Regarding the to be marketed ——— 80 mg tablet, dosing with an AHA meal had little affect on the Cmax, Tmax, or AUC t as compared to dosing the product 2.5 h after a meal.. The systemic availability and Cmax were both higher for the ——— tablet than for the ——— tablet. The lower systemic availability and peak concentrations of the MR tablets could reflect a longer and more sustained exposure of fluvastatin to the liver (increased hepatic extraction efficiency) without saturating the first-pass metabolism.

Study W253-Safety and tolerability and pharmacokinetics of fluvastatin MR-——— Tablet

Title of study: A randomized, double-blind, placebo-controlled, time-lagged, parallel group study to evaluate the safety and tolerability of ascending dose levels of fluvastatin sodium, modified release (Lescol®MR) in subjects with primary hypercholesterolemia (Type IIa/IIb).

Investigator(s): ———

Sub-Investigator(s): See Appendix 2

Number of centers: One

Study period: First subject dosed 03-Nov-1997; Last subject completed 01-Jun-1998

Design: Randomized, double-blind, placebo-controlled, time-lagged, parallel group study.

Number of subjects: Forty

Subjects: Subjects between the ages of 18-55 years with primary hypercholesterolemia (Type IIa/IIb)

Study Design:

A total of 40 subjects with type IIa/IIb hypercholesterolemia were randomized into this study, with ten subjects in each of the 4 treatment groups. Seven of the ten subjects in each group received SDZ XUO 320 (fluvastatin sodium ———) and three subjects received placebo. There was a 21 day screening period, inclusive of a 14-day diet stabilization period, a 14-day treatment period (13 dosing days followed by a 24-hour post-final-dose evaluation), and an end-of-study evaluation, 8 days after the final dose. Each subject received evening doses on each of the 13 treatment days. Doses of 80 mg, 160 mg, 320 mg, and 640 mg were administered to groups 1, 2, 3, and 4, respectively. All doses were administered as multiples of 80 mg ——— tablets in the evening. A period of at least 3 days elapsed between groups 2 and 3 and groups 3 and 4, during which the safety of the prior dose level was reviewed and assessed as satisfactory, prior to proceeding to the next highest dose. Safety and tolerability and evaluations were made at each dose level following a single dose (Day 1) and after multiple doses for 13 days (Day 14). Plasma samples were obtained for pharmacokinetic assessments at 0 hour (Days 1, 2, 4, 7, 10, 12, 13 and 14), and at 1, 2, 3, 4, 6, 9, 12, 16 and 20 hours post-dose (Days 1/2 and 13/14).

Pharmacodynamic assessments in terms of percent change from baseline were also evaluated at each dose level for LDL, HDL, Total Cholesterol, and LDL/HDL at trough (prior to dosing) on days 1, 2, 7, 10, 13 and 14.

Objectives:

Primary: To evaluate the safety and tolerability of multiple rising oral doses of fluvastatin sodium modified release (MR) in subjects with primary hypercholesterolemia (Type IIa/IIb); To assess the pharmacokinetics of multiple rising oral doses of fluvastatin sodium modified release in subjects with primary hypercholesterolemia (Type IIa/IIb).

Secondary: To determine pharmacodynamic effects of multiple rising oral doses of fluvastatin sodium modified release in subjects with primary hypercholesterolemia (Type IIa/IIb); To determine the pharmacokinetic/pharmacodynamic relationship of multiple rising oral doses of fluvastatin sodium modified release in subjects with primary hypercholesterolemia (Type IIa/IIb).

Formulations and Batches Used in Study

Lescol® modified release fluvastatin sodium [redacted] 80 mg (Batch #H-05017)- [redacted] (see study W251 for formulation)

Matching placebo for Lescol® modified release fluvastatin sodium [redacted] 80 mg (Batch #H-05081)

PK variables: Fluvastatin serum concentrations to estimate PK parameters: Median t_{max}(h), $t_{1/2}$(h), C_{max}(ng/ml), C_{min}(ng/ml), AUC_t(h.ng/ml), AUC_∞, AUC_{20}(h.ng/ml), C_{max}^{ss} / C_{max}=Accumulation Factor, CI/f, (C_{max}^{ss} - C_{min}^{ss}) / $C_{av.}$ = Fluctuation Index (where $C_{av.}$ = AUC_τ/τ),

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Analytical Section

Fluvastatin

Serum concentrations of fluvastatin were determined by Bioanalytics & Pharmacokinetics, Novartis Pharma SA, Rueil-Malmaison, France between February 10 and July 20, 1998. [redacted]

was used. For the study samples, all unknown concentrations were calculated from a calibration curve generated from extracted serum standards prepared for each assay run.

A 7-point calibration curve was produced with each analysis run, using serum calibration standards for fluvastatin over the range of [redacted] Four serum Quality Control (QC) sample pools at concentrations of 2, 25, 500 and 2000 ng/ml were also prepared prior to sample analysis and assayed in duplicate on each analysis day. In order to validate the assay of diluted samples, where the initial concentration was above the upper calibration standard, a QC sample with a fluvastatin concentration of [redacted] was prepared. This QC sample was diluted and analyzed in quadruplicate together with the diluted unknown samples.

Summary results for the daily calibration curve parameters and back-calculated standard concentrations from the 28 calibration runs are summarized below:

Summary of fluvastatin calibration parameters and back-calculated concentrations

Calibration Parameters (n = 28)							
Parameter	Mean		Range			%CV	
Slope	[redacted]						
Theoretical and Observed Back-Calculated Serum Concentrations (ng/ml)							
[redacted]	1	5	20	100	250	1000	2500
Mean	[redacted]						
%CV	[redacted]						

Results from the analysis of frozen serum QC samples containing fluvastatin at concentrations of 2.0, 25, 500 and 2000 ng/ml are shown below. For the single "Retest" analysis run, the [redacted]. QC was diluted by 5-fold and assayed in quadruplicate. The results from these analyses were generally consistent with the undiluted QC sample analyses.

Summary of fluvastatin quality control sample analyses

QC Sample Nominal Concentration (ng/ml)	Number of Analyses	Mean Observed Concentration (ng/ml)	Range of Observed Concentrations	Interassay %CV
2.00	59	[redacted]	[redacted]	[redacted]
25.0	60	[redacted]	[redacted]	[redacted]
500	60	[redacted]	[redacted]	[redacted]
2000	60	[redacted]	[redacted]	[redacted]
9580 (dilution)	4	[redacted]	[redacted]	[redacted]

The accuracy of the assay was assessed through the comparison of the mean observed concentrations to the nominal concentrations of fluvastatin in the prepared QC samples. The observed mean values were found to be within [redacted] or less of the nominal concentration for each of the four QC sample concentrations analyzed throughout the course of the study. For the diluted [redacted] QC sample, the mean of the four results was within [redacted] of the nominal value.

The analytical methodology and performance were acceptable for purposes of the study.

Results

Pharmacodynamics

The most reported adverse events were: headache (13 subjects); diarrhea (9 subjects); abdominal pain (6 subjects); and leg pain (6 subjects). Clinically notable LFT elevations occurred frequently in the 640 mg dose group but not at lower doses. As seen in the following table, at least three subjects experienced increases in the LFT measures of SGOT, SGPT, GGT, and LDH in excess of 3 times the upper limit of normal. This may be due to high serum fluvastatin concentrations observed following the 640 mg dose (single dose and multiple doses).

Mean liver function values and number of subjects showing notable changes from baseline (Day -1) per treatment group

	Mean SGOT		# of subjects with SGOT =3 x ULN Table at Day 14 (Subject #)	Mean SGPT		# of subjects with SGPT = 3 x ULN at Day 14 (Subject #)	Mean GGT		# of subjects with GGT = 3 x ULN at Day 14 (Subject #)	Mean LDH		# of subjects with LDH = 3 x ULN at Day 14 (Subject #)
	Baseline	Day 14		Baseline	Day 14		Baseline	Day 14		Baseline	Day 14	
Placebo	16.50	17.17	0	33.33	36.58	0	35.17	34.17	0	126.42	126.34	0
80 mg	17.29	19.72	0	37.29	39.72	0	27.16	33.72	0	140.57	148.14	0
160 mg	17.43	19.72	0	35.71	43.42	0	35.86	42.86	1 (1016)	131.00	135.57	0
320 mg	21.00	26.29	0	42.43	56.57	2 (1021, 1023)	43.14	45.43	0	138.57	151.57	0
540 mg	17.29	262.43	3 (1036, 1037, 1039)	32.86	336.43	4 (1034, 1036, 1037, and 1039)	29.71	152.57	3 (1036, 1037, and 1039)	136.71	361.57	3 (1036, 1037, and 1039)

Triglycerides, total cholesterol, LDL, and LDL/HDL ratio were significantly lower on day 14 compared to baseline, and were also decreased compared to placebo. The data was suggestive of a greater reduction in LDL-Cholesterol than that observed with placebo. There was also a decrease in HDL levels following active treatment. These pharmacodynamic data demonstrated that the fluvastatin ——— tablet was effective both in lowering LDL and total cholesterol in hypercholesterolemia patients following once-a-day administration for 2 weeks.

The mean pharmacodynamic measures (% reduction from baseline) following the 13 day administration of fluvastatin MR once-a-day are listed below.

Mean (S.D) pharmacodynamic measures (% reduction (-) or increase (+) from baseline) following a once-a-day 80-640 mg fluvastatin MR formulation for 13 days (Day 14)

Dose (mg)	Pharmacodynamic measures				
	Triglycerides	Total-C	LDL-C	HDL-C	LDL-C/HDL-C
80	-25 (36.9)	-39 (26.2)	-35.5 (15.8)	-5.4 (8.8)	-30.7 (20.6)
160	-20 (26.0)	-37(6.8)	-47.9 (10.7)	-6.2 (8.0)	-44.4 (10.7)
320	-29 (13.2)	-39 (6.5)	-48.4 (11.1)	-9.3 (12.0)	-43.2 (10.7)
640	-14 (32.3)	-48 (4.4)	-58.6 (7.0)	-24.8 (14.3)	-43.4 (12.5
Placebo	+0.4 (47.6)	-9.8 (8.3)	-12.1 (16.4)	-4.5 (39.7)	+3.8 (35.2)

Results

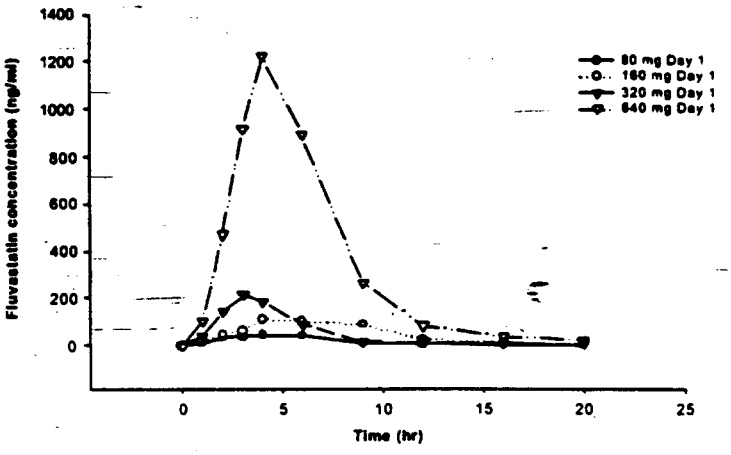
Pharmacokinetics

The single dose pharmacokinetic results are presented in the table and figure below:

Mean ± SD pharmacokinetic parameters of fluvastatin following a single 80-640 mg dose ——— formulation (Day 1).

Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	61 ± 16	162 ± 46	274 ± 134	1388 ±919
Median Tmax (h)	4	4	3.4	4
AUCt (h.ng/ml)	334 ± 124	976 ± 321	1013 ± 489	6854 ± 5333
AUC∞ (h.ng/ml)	349 ± 133	1029 ± 337	1055 ±502	6966 ± 5387
CL/f (ml/hr)	266 ± 119	169 ± 50	388 ± 209	123 ±75
T1/2 (h)	4.5 ± 1.8	4.9±3.1	5.1±2.8	3.6±0.5

Mean serum fluvastatin concentration-time profiles following a single oral dose of 80 - 640 mg [redacted] formulation (Day 1).

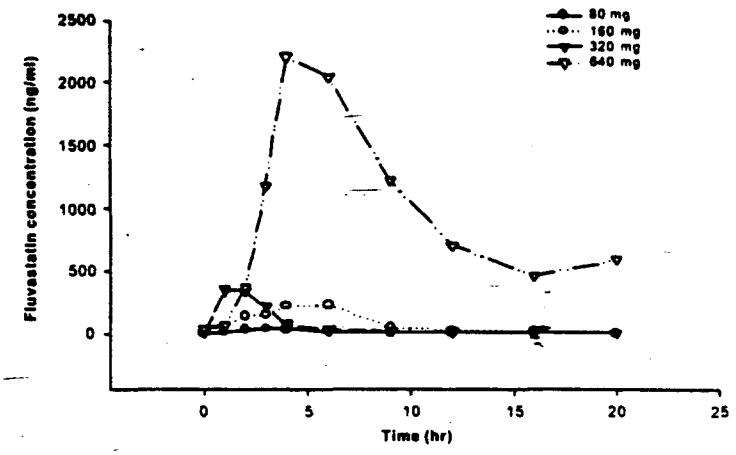


The steady state pharmacokinetic results are presented in the table and figure below:

Mean ± SD pharmacokinetic parameters of fluvastatin following a once-a-day 80-640 mg [redacted] formulation for 13 days (Day 14)

Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	55 ± 27	331 ± 100	586 ± 239	4917 ± 3393
Median Tmax (h)	3	4	4	4
Cmin (ng/ml)	2.8 ± 3.3	7.3 ± 3.6	10.1 ± 7.4	80.7 ± 91.5
AUCt (h.ng/ml)	282 ± 124	1562 ± 486	2744 ± 1645	32189 ± 29339
AUC∞ (h.ng/ml)	361 ± 141 (N=5)	1609 ± 497	2961 ± 1592	42993 ± 40290
CL/f (ml/hr)	345 ± 174	116 ± 54	170 ± 132	39 ± 34
T1/2 (h)	4.7 ± 1.9 (N=3)	3.5 ± 0.9	8.9 ± 12.5	5.4 ± 4.4
Fluctuation Index	4.5 ± 1.2	5.2 ± 1.4	5.5 ± 1.1	4.3 ± 1.4
Acc. Factor	0.91 ± 0.4	2.1 ± 0.6	3.0 ± 2.6	4.9 ± 3.1

Mean serum fluvastatin concentration-time profiles after once-a-day oral dosing of 80 - 640 mg ——— formulation for 13 days (Day 14).



As seen in the table below, nonlinearity in the pharmacokinetics above single doses of 320 mg for the ——— tablet is very evident with a 640 mg dose producing a mean value for AUC 0-00 of 2.5 times of that expected under linear conditions based on the 80 mg dose of the ——— tablet :

Mean dose normalized (value x 80mg/dose) pharmacokinetic parameters of fluvastatin following a single 80-640 mg dose ——— formulation (Day 1).

Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	61	81	69	174
AUCt (h.ng/ml)	334	488	253	857
AUC∞ (h.ng/ml)	349	514	264	870
AUCoo Beyond Expected if linear Dose Normalized AUC t /AUC t 80mg	1	1.5	0.8	2.5

As seen in the table below, under steady state conditions, nonlinearity was evident beyond the 80 mg dosage level for the ——— tablet. Mean values of AUCt ss of 2.8, 2.4, and 14.3 times those expected under linear steady state conditions (based on the 80 mg dose) were seen at the 160, 320, and 640 mg dosage levels.

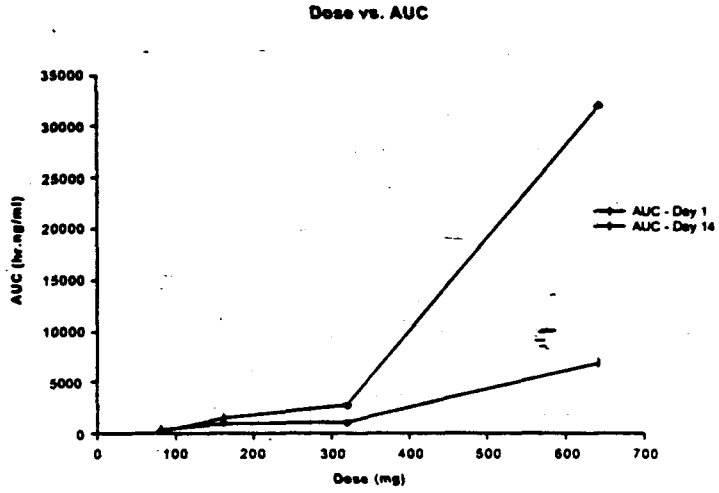
Also as seen in the table below, going from single dose to steady state, nonlinearity was evident beyond the 80 mg dosage level for the ——— : tablets, producing mean accumulation values for AUCt ss/AUCoo sd of 1.5, 2.6, and 4.6 times of those expected under linear single dose to steady state conditions for the 160 , 320, and 640 mg dosage levels. Also of note, average Cmin for the 80 mg tablet was approximately 3 ng/ml which is 3 times the lower limit of quantifiable detection. This indicates that there was some accumulation in this parameter at the 80 mg dose.

Mean dose normalized (value x 80mg/dose) pharmacokinetic parameters of fluvastatin following a once-a-day 80-640 mg ——— formulation for 13 days (Day 14)

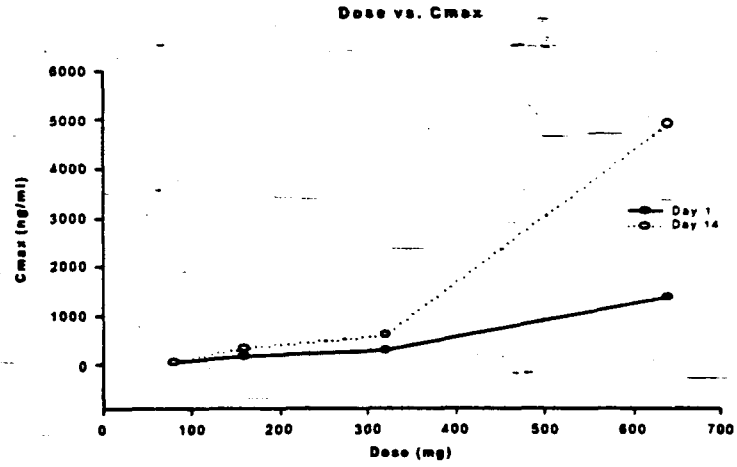
Parameter	80 mg	160 mg	320 mg	640 mg
Cmax (ng/ml)	55	166	147	615
Cmin (ng/ml)	2.8	3.7	2.5	10
AUCt (h.ng/ml)	282	781	686	4024
AUC∞ (h.ng/ml)	361	805	740	5374
AUCt ss Beyond Expected if linear-Multiple Dose Dose Normalized AUCt ss/AUCt ss 80 mg	1	2.8	2.4	14.3
Accumulation Beyond Expected if linear Single Dose to Multiple Dose AUC t ss/AUC oo sd	0.8	1.5	2.6	4.6

The figures below graphically demonstrate the departure from linearity in AUC and Cmax under single dose and steady state conditions over the 80 to 640 mg dosage range for the ——— tablet:

Dose vs mean AUC following a single and multiple doses of 80-640 mg MR formulation.



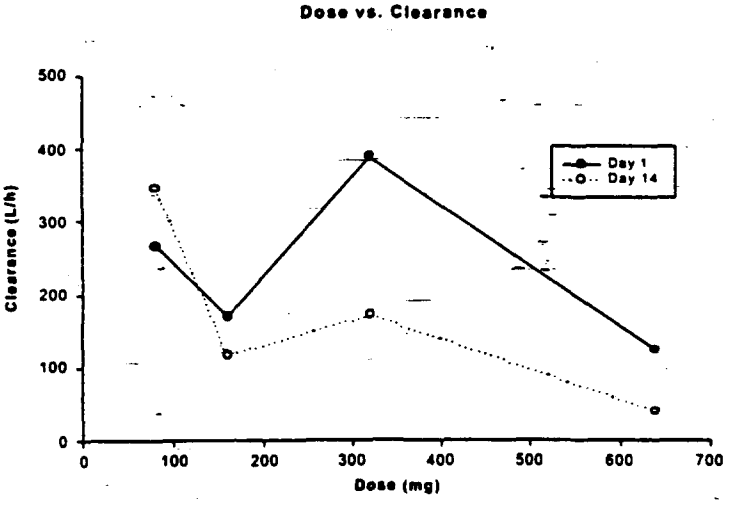
Dose vs mean Cmax following a single and multiple doses of 80-640 mg MR formulation.



Fluvastatin dosed using the ——— tablets possesses both dose and time dependent nonlinear pharmacokinetics. This finding is also consistent with increases in single dose Cmax beyond expected with increasing dose, as well as with increases in steady state Cmax beyond expected based on single doses. Additionally, decreases in clearance with dose and duration of dosing is consistent with dose and time dependent nonlinear pharmacokinetics. ———

The figure below demonstrates pharmacokinetic nonlinearity through the reduction in clearance at the 160 and 640 mg single dose levels as compared to the 80 mg single dose level. The figure also demonstrates pharmacokinetic nonlinearity through the reduction in clearance at steady state at the 160, 320, and 640 dosage levels as compared to the 80 mg dosage level.

Mean fluvastatin CL/f vs dose



Conclusions

- Fluvastatin dosed using the ——— tablets possesses both dose and time dependent nonlinear pharmacokinetics between the 80 and 640 mg dosage levels.
- The ——— formulation produced reductions in LDL-C and total cholesterol at all dose levels.

Study W351-Effect of food on the bioavailability of fluvastatin MR 80 mg tablet

Study synopsis

Title of study: A three-period, open-label, randomised, crossover study to evaluate the pharmacokinetic profile of the fluvastatin sodium 80 mg —— tablet, modified-release formulation under fed and fasted conditions and the intrasubject variability in healthy volunteers

Number of Centers: One

Investigator(s): ——

Study period: First subject dosed 11-Jul-98; Last subject completed: 26-Jul-98

Objectives:

Primary - To determine the effect of food on the pharmacokinetic profile of the fluvastatin sodium 80 mg —— tablet, modified-release (MR) formulation in healthy subjects.

Secondary - To estimate intrasubject variability in the single dose pharmacokinetics of the fluvastatin sodium 80 mg —— tablet, modified-release formulation in healthy subjects.

Design: This study employed a randomised, open-label, balanced, 2 x 2 Latin-square, crossover design with a replicate of the fasting period.

Subjects: Healthy male and female volunteers, aged 18 to 50 years and weighing at least 45 kg and / or within -15% to +15% of their ideal weight.

Sample size: Twenty-four (24) subjects completed.

Investigational drug: XUO-320 Fluvastatin MR Tablets (80 mg) for oral administration
Provided by Novartis Pharmaceuticals
Batch No. T115195,KN # 3745999.000.009 (To be marketed formulation)
Exp 12-31-1998
—— tablet

Treatment strategy: A total of 24 healthy subjects were randomised to one of the two treatment sequences (A or B - see below). After an overnight fast, subjects received a single 80 mg dose of fluvastatin modified release formulation under fasting conditions or with a high-fat breakfast (standard FDA breakfast, with fat comprising approximately 50% of total caloric content of the meal) according to the randomisation schedule (Periods 1 and 2). All subjects repeated a period of drug administration under fasting conditions (Period 3) to assess the intrasubject variability of this MR formulation.

Pharmacokinetic samples were drawn for 24h after each dose (0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 24.0 hrs), and safety evaluations occurred at specified times (0, 2, 4, 6, 8-

hours after drug administration, and at the end of study) during each treatment period. A 3-7 day inter-dose interval occurred between treatment periods.

End-of-study evaluations occurred prior to discharge from the study site in the final period. Subjects were confined to the study center from 12 hours before until 24 hours after each dose.

The treatment design is depicted in the following table:

Treatment Design

	Period 1	Period 2	Period 3
Sequence I	A	B	A
Sequence II	B	A	A

A=Fluvastatin 80 mg ——— tablet MR administered under fasting condition

B=Fluvastatin 80 mg ——— tablet MR administered with a high-fat breakfast (FDA breakfast)

PK variables: Fluvastatin (SDZ XUO 320) serum concentrations, AUC_{24}, AUC_t, AUC, C_{max}, t_{max}, C_{max}/AUC_{24}, $t_{1/2}$

Safety: Physical examinations, vital signs, ECG evaluations, laboratory evaluations and adverse event monitoring.

Statistical Methods: Descriptive statistics for safety and pharmacokinetic variables, with analysis of variance for pharmacokinetic profiles at a 90% confidence interval and an estimate of intrasubject coefficient of variation (under the fasted condition). The effect of food on the bioavailability of fluvastatin MR tablet was assessed based on 90% confidence interval testing. The confidence intervals were determined following analysis of variance of log transformed AUC and C_{max} parameters.

Analytical Section

Serum concentrations of fluvastatin

Serum concentrations of fluvastatin were determined by ——— This method, originally validated for analysis of plasma samples, was cross-validated using human serum ——— . For the study samples, all unknown concentrations were calculated from a calibration curve generated from extracted serum standards prepared for each assay run. This 6 point calibration curve was prepared to cover the range of ——— of fluvastatin.

In order to determine the performance of the assay, four Quality Control (QC) samples were analysed in duplicate in each run. Unknown concentrations above the highest calibrator were validated by analysis of an. extra QC containing ——— . of fluvastatin.

The lower level of quantitative detection was ——— , and the within study accuracy and precision (%CV) were about ——— and ——— at the ——— nominal level and about ——— and ——— at the ——— level.

The assay performance appeared to be acceptable for purposes of analysis of the study's plasma samples for fluvastatin.

Results:

Subject disposition: Twenty-four healthy male and female adult volunteers were enrolled into the study, and 24 completed the study.

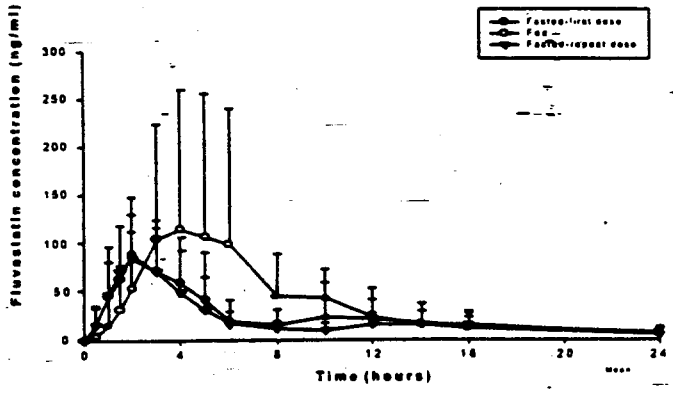
Key demographic data at entry: A total of 12 males and 12 females were enrolled in this study. The mean (±SD) age of these subjects was 29 (± 9) years. The mean (±SD) height and weight measurements were 173(±9) cm and 72 (± 11) kg, respectively.

Safety analysis: It was reported that all subjects tolerated the dose well under fasting and fed conditions. The most frequent adverse events included headache, diarrhea, nausea and general bodyaches.

PK analysis: All comparisons between fasting and fed were made relative to the first dose under fasting condition.

The mean fluvastatin concentration-time profiles are shown below for the two fasted and one fed treatments.

Mean±SD serum fluvastatin concentration-time profiles following a single oral dose of 80 mg MR formulation:



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The mean pharmacokinetic parameters of fluvastatin with and without food are listed below:

Mean ± SD pharmacokinetic parameters of fluvastatin following a single 80 mg dose

MR formulation

(N=24 unless otherwise specified)

Parameter	Fasted - first dose	Fed	Fasted - Repeated dose	90% CI
C_{max} (ng/ml)	126.2 ± 53.3	183.1 ± 163.4	107.2 ± 45.3	0.86-1.51
C_{max} Ratio*	-	1.63 ± 1.27	0.94 ± 0.35	
Median t_{max} (h)	2	6	2	p<0.01
AUCt(h.ng/ml)	578.3 ± 340.9	858.5 ± 632.6	503.4 ± 246.3	1.09-1.78
$AUC_{(0-24)}$ (h.ng/ml)	579.0 ± 340.9	861.1 ± 632.3	505.7 ± 245.5	1.09-1.79
AUC_{24} Ratio*	-	1.74 ± 1.11	0.94 ± 0.28	
AUC∞ (h.ng/ml)	692.8 ± 441.8 (N=14)	1060.0 ± 669.7 (N=17)	611.7 ± 280.5 (N=13)	0.93-1.66
C_{max}/AUC24	0.24 ± 0.07	0.20 ± 0.06	0.22 ± 0.06	
T1/2 (h)	7.0 ± 3.8 (N=14)	4.3 ± 3.2 (N=17)	5.5 ± 2.9 (N=13)	

*Ratios: Mean of ratios relative to the first dose under fasted condition.

Food increased the systemic bioavailability of fluvastatin by approximately 53% from the fluvastatin MR tablet. The 90% confidence interval for AUCo-oo fed vs fasting was 0.93-1.66. Food increased the Cmax by about 45%. The 90% confidence interval for Cmax fed vs fasting was 0.86-1.51. Also, food delayed tmax from about 2 to 6. The mean apparent half-life in the fed group appeared to be somewhat less than that in the fasted group. There was a high degree of variability (CV%) in the Cmax for both the fasted and fed conditions (42% and 89%), but the variability for the fed condition was about twice that of the fasted condition. There was also a high degree of variability for AUCo-oo for both the fasted and fed conditions (64% and 63%).

Intra and Intersubject Variabilities

The mean AUCo-oo and C_{max} values, following a second single dose administration under fasting conditions, were comparable to the first dose under fasting. The mean of individual subject ratios for AUC and Cmax were both 0.94 (CV approximately 30%). The intrasubject variability, based on repeated administrations, was low (CV approximately 22-25%) and much lower than intersubject variability indicating that within-subject performance of the formulation was consistent under fasting condition.

Gender differences:

There were 12 male and 12 female subjects in this study. There was an approximate 45% increase in C_{max} in the fed state relative to fasting in both males and females. There was an approximate 54% increase in AUC in the fed state relative to fasting for males and an approximate 46% increase in AUC in the fed state relative to fasting for females. The mean value for C_{max} in female subjects was approximately 45% greater than those seen in male subjects in both the fed and fasted states. The

mean value for AUC in female subjects was approximately 67% and 77% greater than those seen in male subjects in the fed and fasted states.

Mean ±SD Pharmacokinetic parameters of fluvastatin in male and female subjects following an 80 mg dose

MR ——— formulation

Parameter	Fasted		Fed	
	Male (N=12)	Female (N=12)	Male (N=12)	Female (N=12)
C_{max} (ng/ml)	103.1 ± 37	149.3 ± 59	149.7 ± 121	216.4 ± 197.1
AUC24 (h.ng/ml)	418.6 ± 163	739.3 ± 399	644.2 ± 336	1077.9 ± 788

The extent of variability was high in both groups, similar to that observed in the overall

Conclusions:

- Food greatly increases the systemic availability (C_{max} and AUC) by about 50% for fluvastatin from the 80 mg ——— tablet formulation. In some subjects, the increase in availability and Cmax is substantially greater.
- Fluvastatin concentrations rise rapidly from the ——— tablets fluvastatin. under fed and fasted conditions
- The apparent terminal half-life of the ——— is approximately 2-3 fold longer than that observed for the IR capsule (5 to 7 hours vs. 2.7 hours, respectively)
- The intrasubject variability for the C_{max} and AUC parameters was estimated to be approximately 25%. This was less than the intersubject variability (CV) of approximately 42-64% without food, and 63-89% with food. From this data, it appears that the systemic availability of fluvastatin from the ——— tablet is highly variable, and especially so with food
- Females tend to have a higher C_{max} and a AUC than males

In Vivo Studies Not Reviewed

Comparison of three different fluvastatin modified release formulations and post-prandial effect (W 252)

This study examined the bioavailability characteristics of two [redacted] 80 mg MR capsules (slow release and fast release), one [redacted] tablet and the marketed immediate release capsule under 2.5 h post meal and fed conditions. This study was not reviewed as none of the treatments were identical or similar to the to be marketed formulation.

In Vitro Dissolution

The solubility profile of fluvastatin, Sodium is presented below:

Solubilities of the drug substance (Fluvastatin sodium)

Solubility of Fluvastatin sodium in aqueous solvents at 37°C

Solvent	mg Fluvastatin sodium / mL solvent	Parts Solvent / Parts Solute	Solubility
pH 1.1 Hydrochloric acid	0.076	13158	Insoluble
pH 4.0 Acetate buffer	0.158	6329	Very Slightly Soluble
pH 6.1 Phosphate buffer	1.97	507	Slightly Soluble
pH 7.8 Phosphate buffer	101.0	10	Freely Soluble
pH 9.0 Water, no buffer	169.0	6	Freely Soluble

Fluvastatin sodium is very water soluble, and the current method for the marketed capsules uses [redacted] as the dissolution medium. Although [redacted] could also be used for the modified release tablets, the medium was initially changed to [redacted] since this was more physiologically relevant. [redacted] was chosen since this is typically used for tablets. Drug release was also tested using [redacted] but the rate was markedly slower due to lower solubility at [redacted] Dissolution media at [redacted] was not tested since fluvastatin is almost insoluble at those pHs.

Due to two problems associated with the use of [redacted] was used. Using [redacted] as the medium and [redacted] resulted in much less tablet-to-tablet variability than that with [redacted]

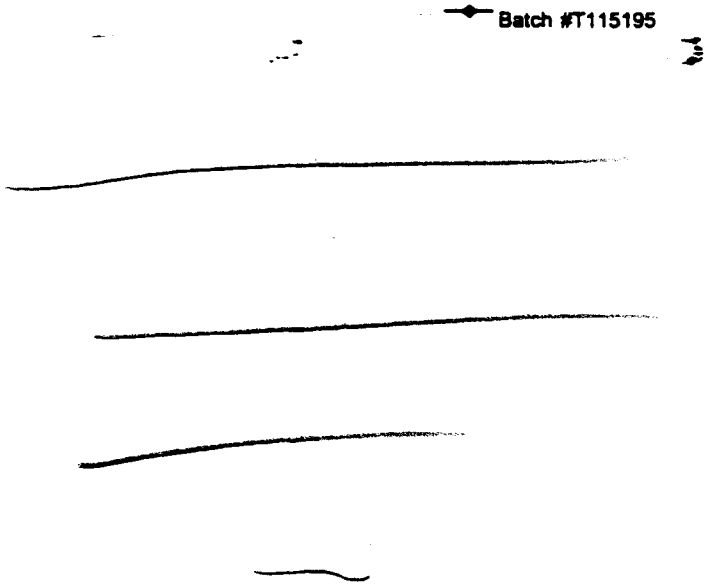
The sponsor reports that in-vivo data suggested a relatively fast release rate of drug substance from the [redacted] tablet, faster than the in vitro data in [redacted] indicated. After an in vitro study evaluating [redacted] and [redacted] with varying buffer concentrations. [redacted] was selected as the medium since it more closely fit the suggested fast release in vivo.

In vitro dissolution profiles of the [redacted] 80-mg fluvastatin MR tablet have been characterized in different dissolution media. The profiles were obtained up to 8 hours using [redacted]

and of each medium. The media included The dissolution profiles are presented below. The dissolution profiles showed that the amount of release was the lowest in the whereas the released amount was maximized in and the percent dissolved was intermediate in Various strengths of showed different degrees of dissolution amounts. Among the media, as the of increased, dissolution decreased suggesting, in part, an ionic effect on fluvastatin dissolution profile.

Comparative dissolution of Lescol XL 80 mg tablets, batch H-05018 ((Batch used in study W251)

Dissolution profile of Lescol XL 80 mg tablet, batch T115195 [redacted] 2, water) (Batch used in study W351)



On average the dissolution in [redacted] showed about [redacted] release in 2 h, about [redacted] release in 4 h and [redacted] dissolution in about 8 hours. Similar dissolution profiles were observed in [redacted] for two different batches (Figures 4.5-1 and 4.5-2). Batch no. H-05018 (clinical trial lot) was tested using [redacted] whereas Batch no. T 115195 (Study W 351) was tested using [redacted] Both methods used [redacted] Although these observations suggest that [redacted] using [redacted] as a medium could be a suitable method for testing dissolution of fluvastatin 80 mg MR tablets, [redacted] was selected for the reasons mentioned earlier.

Individual and mean dissolution data generated using the proposed method and conditions were provided for batches T115195, T116008, T116009, D-01-98, H-05286, H-05287, and H-05290 in a March 1, 2000 submission at the request of OCPB, and mean and range dissolution data for lot H05018 in a September 28, 2000 submission.. This information is contained in Appendix III.

Data for lot H-05018 used in bioavailability study W251 appears below:

Table 2. Dissolution data for Lescol XL Tablets, 80 mg, batch no. H-05018, using method version C

	Cumulative percent release[1]			
Tablet no.				
Average	6.8	26.3	60.1	102.7
RSD (%)	7.4	3.8	4.9	1.3

[1]Data from 24 month stability at 25°C/60%RH stored in a

Data for lot T115195 which was in bioavailability study W351 appears below:

Lescol XL film-coated tablets, 80 mg
Analytical development and justification of specifications JS8012/A

Table 2. Comparison of dissolution data

			Dissolution, average [min, max]			
Batch	Apparatus	rpm				
T115195[1]			7	29	60	98
	% RSD		17.9	22.4	18.5	3.7
			6	26	60	100
	% RSD		11.8	11.2	9.7	0.9

The sponsor reports that the four time points given below were chosen for the specification using The time points evaluate dose dumping and a release of approximately one-third, two-thirds and complete release of the drug substance.

Proposed dissolution limits for fluvastatin sodium MR tablet

Time	Drug released
0.5 hours	
2 hours	
4 hours	
8 hours	

It is reported that the limits were determined by evaluation of dissolution data obtained from in vivo batches, registration stability batches and production batches at time of release and from stability data on these batches. It is reported that based upon these limits, five samples would have gone to Stage 2 testing.

Conclusion – Dissolution

OCPB recommended dissolution limits for fluvastatin sodium MR tablet

Time	Drug released
0.5 hours	
2 hours	
4 hours	
8 hours	

OCPB recommends that dissolution specifications be set based on the lots that were used in the bioavailability studies which were also of the same formulation of those used in the clinical studies. Based on this rationale, the 2 and 4 hour sponsor proposed specification s are too wide and OCPB recommends a 2 hour specification of — and a 4 hour specification of —. OCPB agrees with the 0.5 and 8 hour specifications of —.

Paul L. Hepp, Pharm.D.
Associate Director, OCPB 10-5-00

RD Initialed by ___, Hae Young Ahn, Ph.D.
FT Initialed by ___, Hae Young Ahn, Ph.D.
cc: NDA-21-~~194~~ 192, HFD-510 (Koch), HFD-850 (Hepp,Lesko), HFD-870 (Ahn, ~~Huang~~ Huang,Malinowski,Hunt), HFD-344 (Viswanathan), CDR (for scanning)

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Appendix II-

Sponsor Proposed and OCPB Ammended Labeling

Material changed by OCPB is in highlighted, with new material being highlighted and underlined and sponsor text which OCPB recommended for removal being highlighted and "struck-out.". All of these OCPB changes have been agreed to by the sponsor and the medical reviewing division. The OCPB changes appear in the Clinical Pharmacology, Precautions, and Dosage and Administration sections of the labeling.

Appendix III-

Individual and Mean dissolution data

21 pages redacted from this section of the approval package consisted of draft labeling

Response:

Tables 1 and 2 provide the individual tablet data obtained for Lescol XL Tablets, 80 mg, batch number H-05018, used in clinical study W251. The data presented in Table 1 were obtained using the official methodology at time of batch release (version A in Table 3). Additionally, data are also provided in Table 2 using the dissolution methodology filed in the application (version C). Table 3 describes the three versions of the dissolution method used during the development process.

Table 1. Dissolution data for Lescol XL Tablets, 80 mg, batch no. H-05018, using method version A

	Cumulative percent release						
Tablet no.	0.5 hrs.	1 hr.	2 hrs.	4 hrs.	8 hrs.	12 hrs.	16 hrs.
1							
2							
3							
4							
5							
6							
Average	3.3	6.6	12.8	24.9	48.7	71.6	88.0
RSD (%)	23.4	22.1	22.7	22.6	22.9	22.8	16.5

Table 2. Dissolution data for Lescol XL Tablets, 80 mg, batch no. H-05018, using method version C

	Cumulative percent release[1]			
Tablet no.	0.5 hrs.	2 hrs.	4 hrs.	8 hrs.
1				
2				
3				
4				
5				
6				
Average	8.6	26.3	60.1	102.7
RSD (%)	7.4	3.8	4.9	1.3

[1]Data from 24 month stability at 25°C/60%RH stored in

Table 2. Comparison of dissolution data

Batch	Apparatus	rpm	Dissolution, average (min, max)			
T115196[1]			7	28	60	90
	% RSD		17.9	22.4	16.5	3.7
			8	28	60	100
	% RSD		11.8	11.2	9.7	0.9
T116009[2]			8	32	67	90
	% RSD		15.9	19.8	17.2	3.4
			7	28	62	89
	% RSD		5.4	5.3	5.4	1.3

[1] 3 month, 25C/60% RH sample
[2] Initial sample

The drug release from tablets using the ' was comparable to the release using the which was also at as shown in Figure 2. Since this would facilitate comparison to the earlier ata, the was set at

Figure 2

Lescol MR Tablets, 80 mg - Lot #T116009
Effect on Drug Release Using Different Apparatus

Time (hours)

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The dissolution data presented in Table 1 was obtained using [redacted]
The dissolution data presented in Tables 2-7 was obtained using [redacted]

Table 1. Dissolution of Lescol XL Tablets, 80 mg - Batch #T116196

	Cumulative percent release*			
Tablet no.	0.5 hours	2 hours	4 hours	8 hours
1				
2				
3				
4				
5				
6				
Average	7.8	29.9	62.9	98.3
% RSD	16.0	20.7	18.2	4.3

* Dissolution data obtained using [redacted]

Table 2. Dissolution of Lescol XL Tablets, 80 mg - Batch #T116008

	Cumulative percent release			
Tablet no.	0.5 hours	2 hours	4 hours	8 hours
1				
2				
3				
4				
5				
6				
Average	6.7	26.9	61.7	100.7
% RSD	6.5	8.6	8.7	1.6

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Table 3. Dissolution of Lescol XL Tablets, 80 mg - Batch #T116888

	Cumulative percent release			
Tablet no.	0.5 hours	2 hours	4 hours	8 hours
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	7.1	27.6	62.1	98.9
% RSD	5.4	5.3	5.4	1.1

Table 4. Dissolution of Lescol XL Tablets, 80 mg - Batch #D-01-88

	Cumulative percent release			
Tablet no.	0.5 hours	2 hours	4 hours	8 hours
1				
2				
3				
4				
5				
6				
Average	6.6	27.6	61.1	101.6
% RSD	4.3	7.5	6.3	0.8

Table 5. Dissolution of Lescol XL Tablets, 80 mg - Batch #H-05286

	Cumulative percent release			
Tablet no.	0.5 hours	2 hours	4 hours	8 hours
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	5.8	23.2	50.6	99.2
% RSD	4.9	7.4	9.0	1.4

Table 6. Dissolution of Lescol XL Tablets, 80 mg - Batch #H-05287

	Cumulative percent release			
Tablet no.	0.5 hours	2 hours	4 hours	8 hours
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	5.9	24.1	54.6	100.7
% RSD	6.6	7.4	9.0	1.6

Table 7. Dissolution of Lescol XL Tablets, 80 mg - Batch 9H-05290

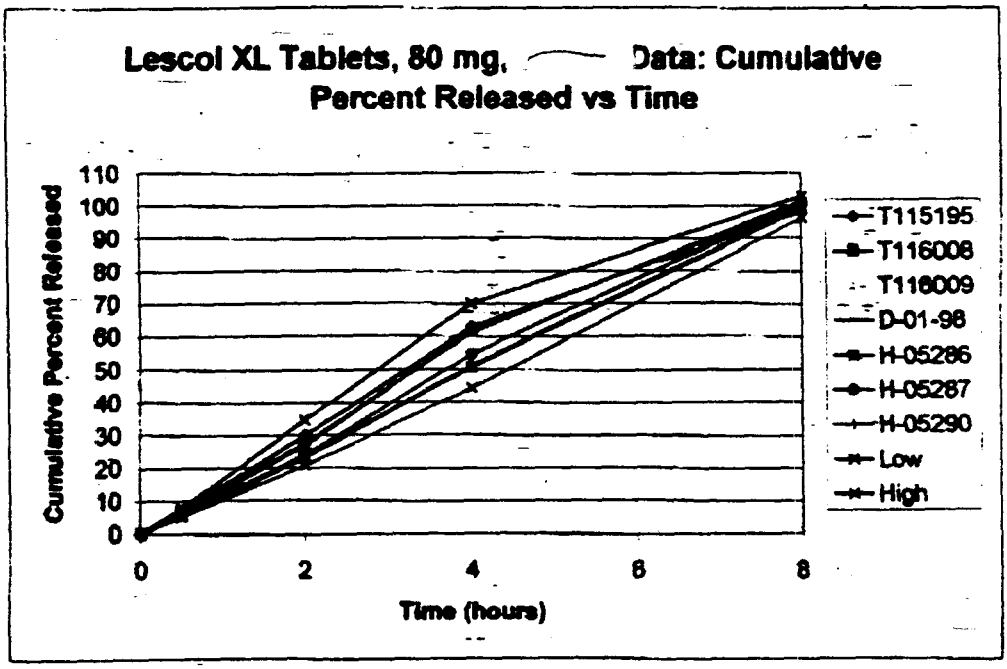
	Cumulative percent release			
Tablet no.	0.5 hours	2 hours	4 hours	8 hours
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	5.7	23.5	51.2	99.5
% RSD	8.9	16.5	13.6	1.6

Lescol XL Tablets, 80 mg
Data and Plot in Response to an FDA Request

Time (hours)	Average Cumulative Percent Released for Seven Batches*							Range for 6 Batches**	
	T115195	T116008	T116009	D-01-98	H-05286	H-05287	H-05290	Low	High
0	0	0	0	0	0	0	0		
0.5	7.0	8.7	7.1	6.6	5.8	5.9	5.7		
2	29.9	26.9	27.6	27.6	23.2	24.1	23.5		
4	62.9	61.7	62.1	61.1	60.6	54.6	51.2		
8	98.3	100.7	98.9	101.6	99.2	100.7	99.5		
# of Tablets	6	6	12	6	12	12	12		

*Batch data, not Range data, are averages of either 6 or 12 tablets for each of the seven batches. Only averages were plotted for each batch. The Low and High data for Range are the individual low and high values at each time interval.

**Note: Range does not include Batch# T115195 since 0-time data for this batch were generated using which is the current method. The range for the lowest and highest individual tablet data was determined using only 0-Time data generated using



Refs.: NB41082D/108 GB, NB82119G/48 CM, NB82119F/103 CM, NB39852G/55 EM, WS1470 LV, WS1472 LV, WS3776 CM

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tablets) and in 50 cc (100 tablets) [illegible] bottles according to a [illegible] design given in the stability protocol addendum. The [illegible] design is complete for either the [illegible] bottles or the [illegible] bottles; however, the designs complement each other to provide a more complete matrix.

Studies to evaluate the effect of light, freezing and refrigeration were also conducted using one batch of tablets.

The following table summarizes the contents of this report.

Packaging	Available data	Batch no.	Site of manufacture	Batch type
US- [illegible] bottles, 30 tabs/60 cc 100 tabs/175 cc	[illegible] long term, [illegible] accelerated	T115185 T116008 T116009	[illegible]	[illegible]
US- [illegible] bottles, 30 tabs/60 cc 100 tabs/175 cc	[illegible] long term, [illegible] accelerated	D-01-98	[illegible]	[illegible]
US- [illegible] bottles, 30 tabs/60 cc 100 tabs/175 cc	[illegible] long term, [illegible] accelerated	H-05286 H-05287 H-05290	[illegible]	[illegible]
US- [illegible] bottles, 7 tabs/30 cc	[illegible] long term, [illegible] accelerated	D-01-98	[illegible]	[illegible]
EU- [illegible] bottles, 30 tabs/15 cc 100 tabs/60 cc	[illegible] long term, [illegible] accelerated	D-01-98	[illegible]	[illegible]
EU- [illegible] bottles, 30 tabs/15 cc 100 tabs/60 cc	[illegible] long term, [illegible] accelerated	H-05286 H-05287 H-05290	[illegible]	[illegible]
Alu/Alu blister	[illegible] long term, [illegible] accelerated	T115195 T116008 T116009	[illegible]	[illegible]

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DEC 27 1999

NDA 21-192 **Date of Review: December 27, 1999**

Sponsor: Novartis Pharmaceuticals Corporation; 59 Route 10; East Hanover, NJ 07936-1080

DRUG LESCOL XL® (fluvastatin sodium) Extended release (80 mg)

CATEGORY: Lipid lowering (HMG CoA reductase inhibitor)

PHARMACOLOGY REVIEW OF NDA 21-192

PHARMACOLOGY COMMENTS: There were no preclinical data submitted under this NDA as agreed at the May 6, 1997 meeting with the sponsor. Lescol is currently approved for use up to 80 mg in the immediate use formulation (recommended 40 mg BID). Original label indicates that most patients will receive 40 mg/day and the multiples in the label reflect this. The labeling for the extended release formulation also indicate that 40mg/day is also the recommended dosage for most patients. Multiples described in the label for the extended release also reflect the recommended dose of 40 mg. No pharmacology review is necessary for this new formulation. There were no labeling changes made to the previously approved preclinical sections of the label.

1-51

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader
12/27/99

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Simoneau
211920.doc
Recommendation code: AP