CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-192

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 21-192 DATE REVIEWED: 09-05-00
CHEMISTRY REVIEW #: 1 REVIEWER: Sharon Kelly

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-08-99	12-09-99	

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corp.
59 Route 10
East Hanover, NJ 07936

DRUG PRODUCT NAME

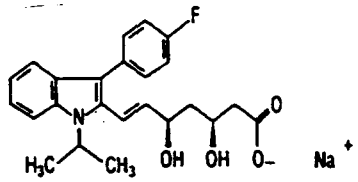
Proprietary:	Lescol XL
Nonproprietary/Established/USAN:	fluvastatin sodium
Code Name/#:	MK-0803, L-154,803-000G
Chem.Type/Ther.Class:	HMG-CoA inhibitor

Patent Status: US 5,354,772 and US 5,356,896 (composition & formulation)

PHARMACOLOGICAL CATEGORY/INDICATION: Lipid lowering agent

DOSAGE FORM: Tablet, extended release STRENGTHS: 80 mg
ROUTE OF ADMINISTRATION: Oral DISPENSED: Rx
SPECIAL PRODUCTS: No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: $C_{24}H_{25}FNO4 \cdot Na$, MW = 433.46
[*R**,*S**-(*E*)] -(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-
-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt.



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

CONCLUSIONS & RECOMMENDATIONS: Satisfactory CMC information has been provided to assure the quality of Lescol XL Extended Release Tablets. From the Chemistry viewpoint the application can be approved, pending an acceptable cGMP inspection.

cc:
Org. NDA 21-213
HFD-510/Division File
HFD-510/SKelly
HFD-510/MSimoneau
HFD-510/SMoore
R/D Init by: Team Leader

Sharon Kelly, Review Chemist

AE

9/12/00

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Statistical Review and Evaluation

SEP 18 2000

NDA:	21-192
Sponsor:	Novartis
Drug:	Lescol (fluvastatin sodium)
Indication:	80mg modified release dose for hypercholesterolemia
Documents reviewed:	Volume 1 dated 12/9/99, electronic submission dated 12/9/99
Medical Reviewer:	Shaio-Wei Shen, M.D. (HFD-510)
10-month User Fee date:	October 9, 2000

The sponsor has submitted three 24-week randomized, controlled, double-blind, parallel group clinical trials in support of a modified release (MR) 80mg dose of Lescol (fluvastatin) for hypercholesterolemia.

The three controlled trials conducted by the sponsor are shown in Table 1. All three trials compared Lescol MR 80mg to Lescol IR 40mg in identical populations. Two of the trials (302, 353) also had a third treatment arm, Lescol IR 40mg bid. The MR 80mg dose demonstrated greater reductions in LDL-C percent change from baseline, the primary endpoint, compared to IR 40mg. Treatment differences were statistically significant in all three trials ($p<.001$). Between treatment differences in least square means were -8.3%, -8.0% and -10.1% in Trials 302, 351 and 353, respectively, all greater than the 6% difference the Division requires for effectiveness when doubling a dose. The MR 80mg dose also demonstrated comparable reductions in LDL-C percent change from baseline compared to IR 40mg bid. Between treatment differences in least square means were +0.1% (favoring IR 40mg bid) and -2.5% (favoring MR 80mg) in Trials 302 and 353, respectively.

This review was written in response to questions raised by the reviewing medical officer concerning a secondary endpoint, HDL-C. The review is intended to clarify the clinical trial results and the sponsor's label claims concerning this endpoint.

Table 1. Summary of clinical trials of Lescol MR 80mg

Study # (dates)	# of centers (country)	Treatment/dose [1]	# of pts randomized	Treatment periods
XUO-F302 (4/98-5/99)	51 (9 European countries)	Lescol MR 80mg Lescol IR 40mg Lescol IR 40mg bid	341 174 171	4 weeks SB diet + placebo 24 weeks DB
XUO-F351 (2/98-4/99)	30 (US)	MR 80mg IR 40mg	369 183	4 weeks SB diet + placebo 24 weeks DB
XUO-F353 (3/98-4/99)	29 (International, 6 countries incl US)	Lescol MR 80mg Lescol IR 40mg Lescol IR 40mg bid	139 143 152	4 weeks SB diet + placebo 24 weeks DB

[1] MR = modified release, IR = immediate release

Results

Table 2 shows HDL-C results for the three studies.

Table 2. HDL-C results for the ITT populations [1]

	MR 80mg	IR 40mg	IR 40mg BID
Study 302	n=341	n=174	n=173
Baseline mean (mg/dL)	53.3	54.7	51.5
Least squares **mean** % change	8.1	6.2	6.7%
Treatment difference with MR 80mg [2]		-1.9	-1.4%
		(p= .16)	(p= .29)
Standard dev	17.7	16.4	16.0
Median % change	6.8	6.1	5.2%
Study 351	n=369	n=183	
Baseline mean (mg/dL)	50.4	48.6	
Least squares **mean** % change	8.6	7.2	Na
Treatment difference with MR 80mg [2]		-1.4	
		(p=.24)	
Standard dev	15.4	13.5	
Median % change	6.9	5.9%	
Study 353	n=139	n=143	n=152
Baseline mean (mg/dL)	51.5	52.6	50.5
Least squares **mean** % change	10.8%	4.6%	7.3%
Treatment difference with MR 80mg [2]		-6.2%	-3.5%
		(p< .001)	(p= .008)
Standard dev	12.7	12.4	12.3
Median % change	9.0%	3.7%	6.0%

[1] The intent-to-treat population was defined as all randomized patients who had a baseline observation and at least one observation following randomization. The Table uses the last on-study observation from each patient (LOCF data).

[2] The statistical model was ANOVA with fixed-effects for treatment group and center.

In Trial 353, HDL-C percent change from baseline was significantly greater for MR 80mg compared to IR 40mg given once a day ($p<.001$). The differences in HDL-C between these treatment groups were not statistically significant in Trials 302 and 351 ($p \geq .16$). The significant results for Trial 353 (vs non-significant statistical results for Trials 302 and 351) were the result of both a larger effect size and smaller standard deviation. (The sponsor reported standard errors (SE) rather than the standard deviations (SD) shown in the Table. Reporting SEs obscures the greater variability for MR 80mg since larger sample sizes for this dose (Trials 302 and 351) will produce smaller SEs, i.e., $SE = SD/n^{1/2}$.)

Figure 1 shows distributions of HDL-C responses in Trial 302 as measured by the percent change from baseline using the LOCF data. The box of the box and whisker plots gives the median and interquartile range (75^{th} minus 25^{th} percentile). The whiskers are 1.5 x the interquartile range. Values beyond the whiskers are considered outliers and are denoted by circles.

Tests of normality were performed for each treatment group. Only the data for the MR 80mg treatment group was signifcantly non-normal (Shapiro-Wilk test, p=.001).

Figures 2 and 3 show box and whisker plots for Trials 351 and 353, respectively. The data in each treatment group and for each study are approximately normally distributed.

Table 2 and Figures 1-3 illustrate the slightly greater uncertainty in response for MR 80mg compared to IR 40mg and IR 40mg bid. Standard deviations were numerically higher for MR 80mg compared to the IR dose groups in all trials. Also, Trial 302 had a significantly greater number of outliers in the MR 80mg group. The percentage of outliers in the MR 80mg group (n=31, 9%) was at least triple the percentages in the IR dose groups (3% for qd and <1% for bid).

Pooled data

The sponsor pooled the results of Trials 302, 351 and 353 for LDL-C and all secondary endpoints, including HDL-C (Table 3). HDL-C percent change from baseline was significantly greater for MR 80mg compared to IR 40mg (ANOVA, p<.001). A nonparametric analysis yielded a p-value of .015. The comparison between MR 80mg and IR 40mg bid did not reach statistical significance (ANOVA p=.062, rank analysis p=.17). The nonparametric analyses are more appropriate due to the non-normality of the pooled data. The significant statistical difference between MR 80mg and IR 40mg can largely be attributed to the significant result in Trial 353.

Table 3. Pooled HDL-C results for the combined ITT populations

	MR 80mg n=849	IR 40mg n=500	IR 40mg bid n=325
Baseline mean (mg/dL)	51.8	51.9	51.0
Least squares **mean** % change	8.3%	5.6%	6.6%
Treatment difference with MR 80mg [1]		-2.7% (p< .001) [2]	-1.7% (p= .062) [3]
Standard dev	13.7	13.2	13.9
Median % change	7.1%	5.3%	5.7%

[1] The statistical model was ANOVA with fixed effects for treatment group and study.
[2] p=.015 if observations are replaced by ranks in the analysis (nonparametric analysis)
[3] p=.17 if observations are replaced by ranks in the analysis (nonparametric analysis)

Comments and suggestions for labelling

The label has been amended primarily by adding data from the pooled results for the MR 80mg treatment groups; individual study results are not presented. The sponsor cites two sets of results for HDL-C: the percent change from baseline for completers (in the text) and the median, also for completers but described as "Week 24 endpoint" data (in the Table). Results are presented descriptively without accompanying p-values or confidence intervals. ITT results are not shown.

Is it appropriate to pool results of the three studies? An argument in favor of pooling can be made by noting that the patient populations and study designs are identical. However, only one of the three studies provided strong statistical evidence favoring MR 80mg over IR 40mg. Because the HDL-C results of the studies are quantitatively different, although not qualitatively so, one could question whether the pooled result is reflective of the evidence from the individual studies. In this reviewer's opinion, since no statistical significance is attached to the pooled data, the use of the pooled MR 80mg data in labelling is satisfactory with the following additional suggestions/comments.

- Descriptive statistics for HDL-C should be presented as medians, not simple averages or least-square means, due to the non-normality of the pooled MR 80mg data.

- In general, labels should emphasize ITT results as opposed to results for completers. Because the median HDL-C percent change from baseline is the same for both completers and ITT populations, use of completers data in the Table (which is consistent with the data in the Table from previous trials) is acceptable.

- The sponsor presents HDL-C results for two subgroups of the MR 80mg treatment group, patients with baseline HDL-C <35 mg/dL (n=35) and patients with both baseline TG≥200 mg/dL and HDL-C <35 mg/dL (n=22). These subgroups represent relatively small percentages of the total number of subjects randomized to MR 80mg (4% and 3% out of 849 patients, respectively). It is left to clinical judgment whether the small numbers of patients per subgroup are sufficient to justify the addition to the label.

Conclusion

For the HDL-C data, the median is the most appropriate statistical measure for descriptive purposes. The label should be modified accordingly.

/S/

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius /S/

Cc:
Arch NDA 21-192
HFD-510/WKoch
HFD-510/DOrloff, SShen
HFD-715/TSahlroot, DB2
Chron

This reviews contains 4 pages of text and 2 pages of graphs.

Figure 1

Trial 302

Week 24/ endpoint HDL % change

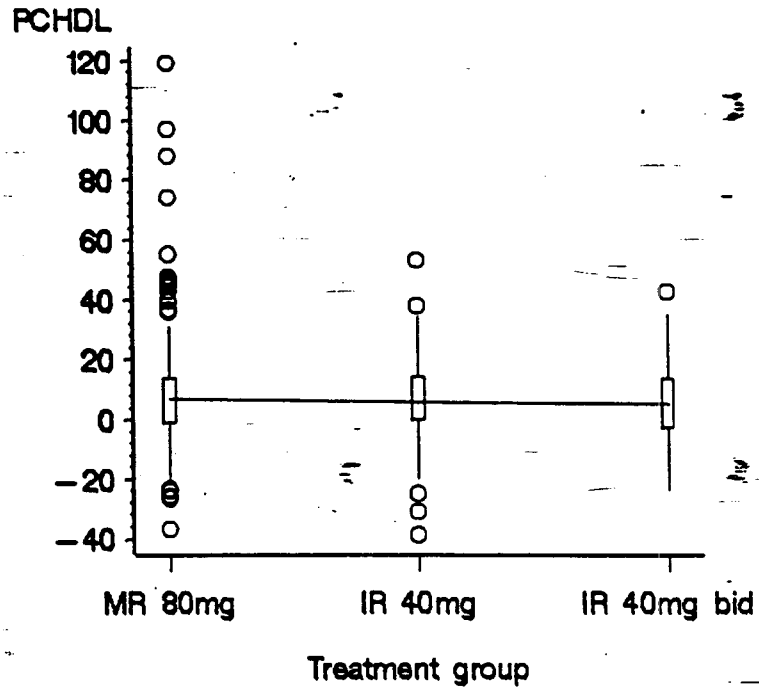


Figure 2

Trial 351

Week 24/ endpoint HDL % change

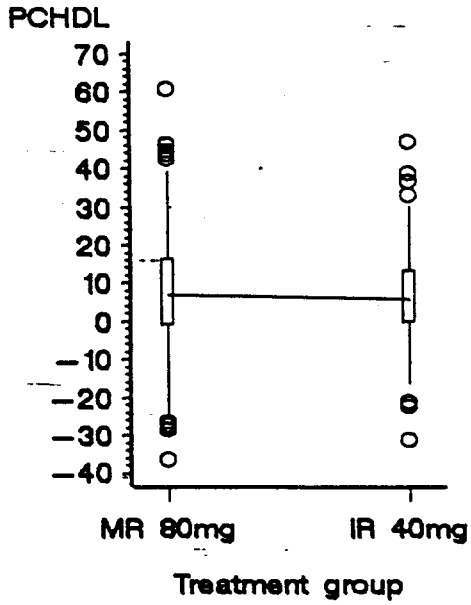
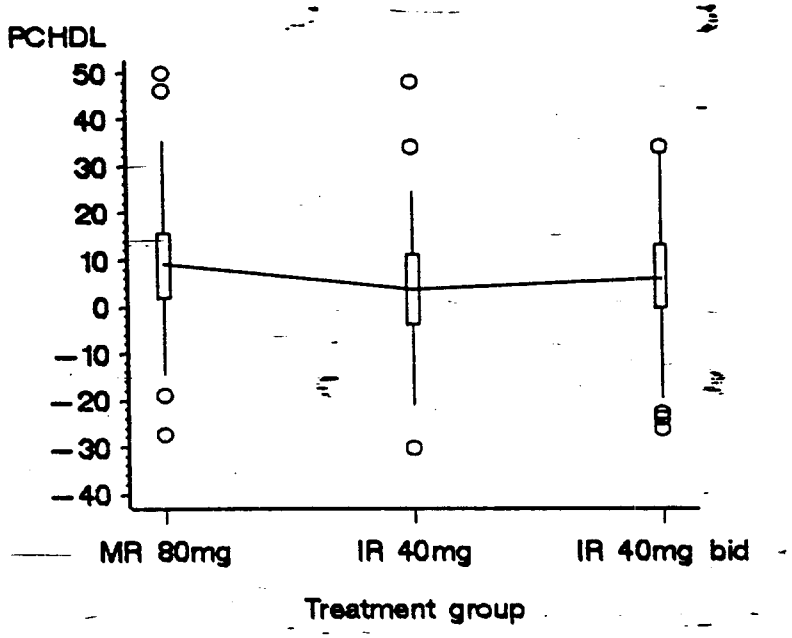


Figure 3

Trial 353

Week 24/ endpoint HDL % change



Team Leader's Statement for NDA 21-192, Lescol XL

There was a meeting held on 10/3/00. In the meeting Larry Lesko, Henry Malinowski, John Hunt, Paul Hepp and myself discussed about a steady state bioavailability study as a phase 4 commitment, that was recommended by Paul Hepp.

In the meeting it was decided that **a phase 4 commitment be not needed** because there are no scientific reasons for us to believe that Lescol XL will be accumulated after multiple dosing. Although the regulations (21CFR 320.25f) state that a steady state bioavailability study for extended release products is needed and the study has not been conducted by the sponsor, it was concluded that a steady state bioavailability study may not have any significant impacts on the quality of the drug product. The decision was made based on the following reasons:

1. A multiple dose bioavailability study was conducted with the ——— tablets of which the input rate is slower than that of the ——— tablets, Lescol XL, and showed no accumulation. Composition of the two ——— tablets is exactly same except the ratio of ——— and Hydroxypropyl methylcellulose.

2. Individual plasma profiles after singe doses of the to-be-marketed product showed no significant trough levels after 24 hours.

3. Apparent elimination half-life of the product is about 4-7 hours. There seems to be absorption rate-limited elimination (flip-flop) since an immediate release product has an elimination half-life of 2.5 hours. Since accumulation is dependent on elimination half-life and dosing interval, there is no reason for us to believe that accumulation occurs for the extended product, Lescol XL.

4. In addition, 3 clinical trials were conducted. There was no safety issue. If market access were based on pharmacokinetics alone, then a steady state bioavailability study would be needed in lieu of efficacy data as additional support for approval.

5. Out of 3 clinical trials, two clinical trials were 3 treatments, parallel studies including immediate release 40 mg qd, immediate release 40 mg bid and Lescol XL 80 mg qd, and it has been found that Lescol XL qd is non-inferior to immediate release 40 mg bid.

6. The approved current labeling indicates that Lescol immediate release product shows no accumulation upon multiple dosing.

Hae-Young Ahn, Ph.D., Team Leader, DPE II, OCP 1/5/01

Henry Malinowski, Ph.D., Acting Division Director 1/5/01