CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19922

STATISTICAL REVIEW(S)

Z. McDonald

Statistical Review and Evaluation

JUN 16 1997

NDA:	NDA 19-922
Date of Document Received by CDER:	June 26, 1996
Applicant:	Neurex Corp.
Name of Drug:	Corlopam (fenoldopam mesylate)
Indication:	Hypertension
Statistical Reviewer:	Kun Jin, DBI/OEB, HFD-710
Medical Reviewers:	Abraham Karkowsky and Steve Rodin, ODE I, HFD-110

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1. Introduction:

This review provides a more detailed report on the statistical analysis of study #94-05 and it supplements the joint medical, statistical and biopharmaceutical review of NDA 19-922. (See the joint review for more details of this NDA.)

Study #94-05 is a pivotal study that defines the effect of fenoldopam in patients with mild to moderate hypertension. The statistical portion of the clinical trial of study #94-05 was handled by two CRO groups: The sponsor's analyses are mainly descriptive statistics and simple linear regressions at the different time points.

This reviewer has performed an independent analysis on the data sets provided by the sponsor. The model used in the analysis is a linear mixed-effects model (also called random-effects model) that included terms for dose, time (to define tolerance), between individuals random effect and within individuals random error. The random-effects model was chosen because the measures from same individuals (at different time) were used in the analysis. The between individuals random effect included a linear random effect and a non-linear (circadian rhythm) random effect. The final model has been validated by several goodness-of-fit criteria.

2. Study Design and Description:

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study. On day one, the patients received a 24-hour intravenous (IV) infusion of vehicle-only solution. On days two and three, the patients received placebo or one of 4 fenoldopam doses (0.04, 0.1, 0.4, 0.8 ug/kg/min) administered by constant-rate, fixed-dose IV fenoldopam infusion without titration. On day four, patients again received a 24-hour IV infusion of vehicle-only solution. During the 4-day period, patients' blood pressures and heart rates were monitored by every 15 minutes, with the exception that during the first hour after the start (day one) and the stop (day four) of study-drug infusion the monitoring was done by every 5 minutes.

Thirty-five patients were randomized to 1 of 5 groups (four fenoldopam, 1 placebo). Thirty-three of the 35 randomized patients were qualified for the active-treatment phase of the study. Thirty-two patients completed the entire 4-day study period. One patient withdrew at the end of the day 3. One patient who received a wrong dose, 0.01 ug/kg/min, was excluded from this analysis. The breakdown of the 32 patients used in this analysis are as follows:

Table 1

Group	Placebo	0.04 u/k/m	0.1 u/k/m	0.4 u/k/m	0.8 u/k/m
Number of patients	7	7	7	5	6

According to the sponsor's report, there were 3 randomization errors occurred in the dose assignment to the 32 patients. Two errors were made at the site in communication between a study pharmacist and the randomization center at . One patient,

randomized to receive a placebo, instead received 0.8 ug/kg/min of fenoldopam. The other patient, randomized to 0.4 ug/kg/min of fenoldopam, instead received a placebo. A third patient was randomized to receive 0.4 ug/kg/min but instead received a dose of 0.04 ug/kg/min due to a transcription error made by . . . . . The dose groups in this analysis refer to the actual doses received by the patients. The baseline measurements of those dose groups will be compared.

3. Data Sets:

The statistical analysis was based on the data sets provided by the sponsor. This reviewer assumed that the data sets and their descriptions represent the accurate records from the trial.

The data sets consist of records of all patients including demographies, dose, time, diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) over a four-day period. The original observations of 32 patients are plotted in Figures A1-A3 of Appendix.

The general impression from Figures A1-A3 is that there are excessive variations present in the data. The drug visibly lowers the patient blood pressures, particularly in the high dose groups. There are missing values at some time points, but they do not seem to affect the dynamic nature of the response curves, nor the drug effects. In the following analysis no particular attempt was undertaken to amend the missing value's problem. It was assumed that they were missing completely at random.

This reviewer has found that there were about 1-2 hours delays from the end of the vehicle infusion to the start of the active drug infusion. This might be the reason for the significant treatment effect at the time zero of day two in the sponsor's report that caused a confusion among the reviewers. This reviewer has rescaled the times to sequential time points and set the start time of active drug infusion as time zero.

4. Local Smoothing and Baseline Adjustment:

The daily measurements of a patient blood pressure and heart rate have a cyclical variation caused by patient's circadian rhythm. We adopted a common approach to adjust patients' BP or HR measurements by their baselines, namely, each measurement at the treatment phase was subtracted by the corresponding values at the same clock time of the baseline infusion for same individual.

There were large variations in the measurements even at adjacent time points. Adjustment of baseline using original data seems to be problematic. Often there are no exact corresponding clock time points in the baseline, sometimes one of two adjacent time points could be chosen as the approximate clock time point. The adjusted results with respect to different time points could be quite different due to large baseline fluctuations at adjacent time points. The adjustment on the original data might produce a data with even larger variations. To reduce the variation, we first smooth the data locally by taking median of measurements, X_j, of measurements from the time interval [j*60 min, (j+1)*60 min) as a representative for that interval, j = -24, ... , 71. Figure 1 shows two patients' original diastolic blood pressure curves and their smoothed versions. It can

be seen that the transformed curves are smoother with less variations. A common concern with the smoothing is that it might result in a loss of signals in the data. From Figure 1, we see that the

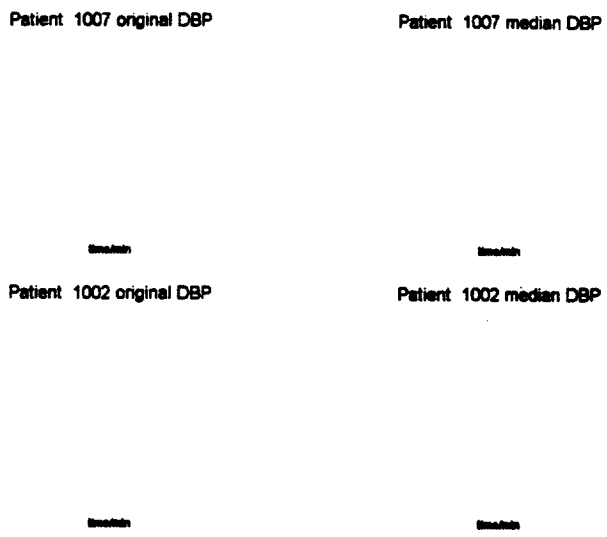

Figure 1 Two original diastolic blood pressure curves (right side) and their locally smoothed curves (left side).

smoothed curves preserve the dynamic nature of the original curves. The adjustment was done on the smoothed data, X_j.

The adjusted treatment phase observations will be

$$\begin{aligned} Y_j &= X_j - X_{j-24} && 0 \le j < 24 \\ &= X_j - X_{j-48} && 24 \le j < 48 \\ &= X_j - X_{j-72} && 48 \le j < 72 \end{aligned}$$

In the following sections, X_j and Y_j will be used to denote a diastolic blood pressure, systolic blood pressure or heart rate interchangeably. The adjusted value Y_j represents the change of patients' measurement in the treatment phase from his (or her) own baseline.

5. Comparison of Baseline:

We first tested whether the baseline measurements of different treatment groups were statistically different. Let X_{ijk} be the baseline measurement (DBP, SBP or HR) of ith patient in k dose group at time t_j, k = 0, 0.04, 0.1, 0.4, 0.8, i = 1, ... , n_k, $t_j = j + 0.5$, j = -24, ..., 71, where t_j is the midpoint of jth time interval. We fitted the following linear mixed-effects model to the baseline data,

$$(1) \qquad X_{ijk} = u_k + a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24) + c_i + e_{ijk},$$

where u_k represents average of baseline measurements for dose k group, (a_i, b_i, c_i)'s (i = 1, ... , n_k, k = 0, 0.04, 0.1, 0.4, 0.8) are iid random vectors with a normal distribution of N(0, B), B is a 3 by 3 unknown covariance matrix. The random effect $a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24) + c_i$ represents a between-subject variation for ith patient and it takes account of the variation of ith

patient from the group mean u_k. e_{ijk}'s are iid random measurement errors with a normal distribution $N(0, \sigma^2)$ with unknown variance σ^2. See the following section for detail description and explanation of the linear mixed-effects model.

To compare the baselines of different groups, we carried out a log likelihood ratio test for H_0: $u_0 = u_{0.04} = u_{0.1} = u_{0.4} = u_{0.8}$ vs $(u_0, u_{0.04}, u_{0.1}, u_{0.4}, u_{0.8}) \in \mathbb{R}^5$. The p-values under H_0 are as follows,

Table 2

Baseline Measurement	DBP	SBP	HR
p-value	0.951	0.672	0.999

We also did a simple test to compare the baseline DBP, SBP and HR among different dose groups. We extracted 25th, 50th and 75th quantiles from each patient original baseline DBP, SBP and HR measurements and then run an ANOVA test on the same type of quantiles separately. The following are the p-values from these tests.

Table 3

Quantiles		25th	50th	75th
P-values	DBP	0.81	0.97	0.96
	SBP	0.62	0.63	0.59
	HR	0.97	0.91	0.94

From the above analyses, we see that there is no statistically significant difference in baseline DBP, SBP, HR measurements among the different dose groups.

6. The Purposes of Statistical Analysis of Steady State Response:

The main purposes of the statistical analysis is to evaluate the patient response to fenoldopam at the steady state. After discussion with the medical reviewers, the patients will be considered in steady state one hour after the fenoldopam infusion. The adjusted treatment measurements, Y_j's ($j \geq 1$), were used in the analysis. The statistical analysis will attempt to answer 1) whether responses of fenoldopam patients are significantly different from that of placebo patients; 2) whether there is a tolerance in fenoldopam patients' response, i.e., whether the patient's response to fenoldopam diminishes with time. The statistical analysis will also provide the estimates of patients' responses at the given time points for each dose group.

7. Graphs of Baseline Adjusted Responses:

The means and standard errors of baselines adjusted DBP, SBP and HR for each dose group at different time points were calculated and plotted against that of placebo group in Figures 2-4.

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From these plots, we can see that fenoldopam reduces patient blood pressure, particularly in high dose groups. It seems that the drug effect diminishes with time, at least for the high dose groups.

8. Linear Mixed-Effects Model:

To carry out a statistical inference, we fit the following linear random effects model to the changes of the measurement (DBP, SBP, or HR) from baseline:

$$(2) \qquad Y_{ijk} = u_k + \beta_k t_j + a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24) + c_i + e_{ijk},$$

where Y_{ijk} is the change from baseline of measurement (DBP, SBP or HR) of ith patient in k dose group at time t_j, k = 0, 0.04, 0.1, 0.4, 0.8, i = 1, ... , n_k, $t_j = j + 0.5$, j = -24, ..., 71, where t_j is the midpoint of jth time interval. Notice that i is actually i(k) which is always nested in the kth group, we use i to simplify the notation. $u_k + \beta_k t_j$ is the fixed-effect of dose k (ug/Kg/min) group. u_k represents average change of measurement from baseline for dose k group without taking account of time effect; β_k represents the time effect for dose k group, a positive β_k means that the drug effect diminishes over time, i.e., a tolerance. $a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24) + c_i$ is the random-effect component for ith patient, where (a_i, b_i, c_i)'s (i = 1, ... , n_k, k = 0, 0.04, 0.1, 0.4, 0.8) are iid random vectors with a normal distribution of N(0, B), B is a 3 by 3 unknown covariance matrix. The random effect $a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24) + c_i$ represents a between-subject variation for ith patient, and it takes account of the variation of ith patient from the group fixed-effect, $u_k + \beta_k t_j$. $a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24)$ represents a cyclical random effect and c_i a linear random effect. e_{ijk}'s are iid random measurement errors with a normal distribution $N(0, \sigma^2)$. (a_i, b_i, c_i)'s and e_{ijk}'s are independent. See Laird and Ware (1982) and Lindstrom and Bates (1988) for a general reference on linear random effects models.

8.1 The Choice of Model: DBP as an Example:

Here we use the changes in diastolic blood pressure as an example to show how the model (2) was chosen. With only 32 patients in the study, we have to keep the number of parameters in the model as few as possible, otherwise the model will be over fitted. The linear fixed effect parameters (u_k, β_k) (k = 0, 0.04, 0.1, 0.4, 0.8) are minimum number of parameters needed to answer clinical question whether there are treatment effects and tolerance. This is a repeated measures' problem, i.e. the observations from same individual are dependent. It is known that this type of data would be better fitted with a random effects model. The first model this reviewer considered was

$$(3) \qquad Y_{ijk} = u_k + \beta_k t_j + c_i + e_{ijk}.$$

To see the necessity of introducing the random effects model, let's compare the fitted results of the model (3) with that from an ordinary linear model

$$(4) \qquad Y_{ijk} = u_k + \beta_k t_j + e_{ijk},$$

which ignores the dependent nature of the data. Table 4 presents these results:

Table 4 Comparison of linear and random effects model with DBP data.

	Linear Model			Random Effects Model		
	Value	Std. Error	t-value	Value	Std.Error	zratio
u_0	-1.64	0.57	-2.89	-1.64	1.96	-0.84
$u_{0.04}$	-7.44	1.17	-6.36	-7.44	2.15	-3.45
$u_{0.1}$	-12.88	1.17	-11.01	-12.88	2.15	-5.98
$u_{0.4}$	-21.83	1.39	-15.73	-21.91	2.55	-8.59
$u_{0.8}$	-20.07	1.28	-15.74	-19.91	2.33	-8.54
$\beta_{0.04}$	-0.13	0.04	-3.01	-0.13	0.04	-3.46
$\beta_{0.1}$	-0.10	0.04	-2.41	-0.10	0.04	-2.78
$\beta_{0.4}$	0.16	0.05	3.30	0.17	0.04	3.90
$\beta_{0.8}$	0.10	0.05	2.24	0.10	0.04	2.44

The main difference of the two models is in their estimates of standard errors. With the ordinary linear model, the SE's are underestimated, and even the intercept of placebo group is "significantly different" from zero. A more objective way to check the models would be to look at their residuals, e_{ijk}'s, which are supposed to be iid normal random variables. We lined up all the residuals by grouping the residuals from the same patients together and keeping them in the same time order. We then plot these residuals against equally spaced points in a horizontal axis. The normal residuals should fluctuate around zero without a systematic pattern. We also plot the autocorrelation function of the lined residuals with a maximum lag of 48. The normal residuals, "white noise," should produce only one significant peak at the zero lag. Figure 5 shows the plots of residuals and autocorrelation function from the two models. It is easily seen that the model (3) fits the data much better than the ordinary linear regression model.

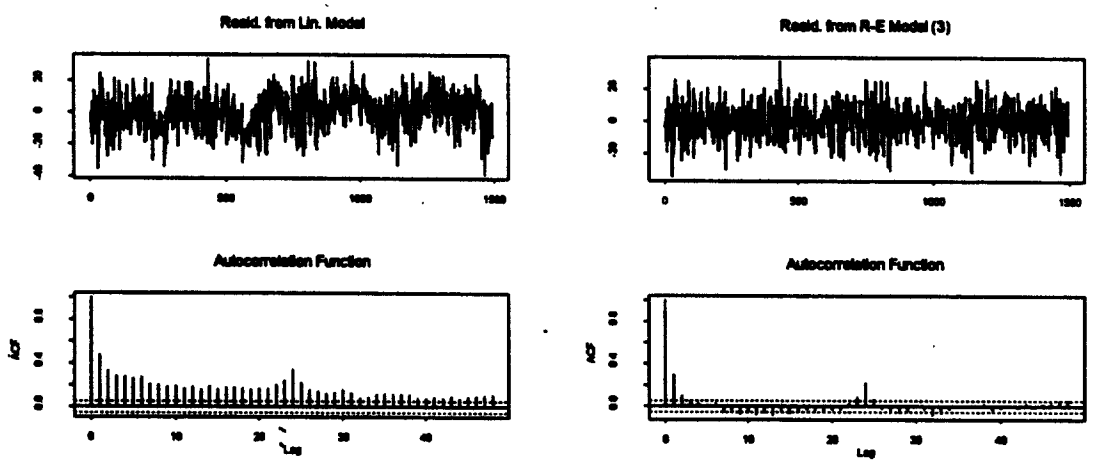

Figure 5 The plots on the left side are the sequential plot and autocorrelation function of the residuals from the simple linear model; the right side are that from the random effects model (3)

Although the model (3) fits the DBP data better, it is still in a linear form. The changes of DBP over time are apparently in non-linear form and there are still cyclical variations in spite of the adjustment by baseline. With the small number of patients in each dose group, it is not practical to fit the data with more non-linear parameters as fixed effects. A non-linear random effect component, $a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24)$, would be an ideal addition to the model (3). Since $a_i \cos(2\pi t_j/24) + b_i \sin(2\pi t_j/24)$ is equivalent to $a_i^* \cos(2\pi t_j/24 + \phi_i)$, this random-effects component will be able to account for the individual cyclical variations from the group fixed-effects. This consideration leads to the model (2) in the previous section. The residual plots for this model are in Figure 6, and it can be seen that they are more close to normals. This model has AIC (Akaike's Information Criterion) of 10795.81 v.s. 10900.44 for the model (3). The substantial reduction in AIC provides a further support for the model (2). See Jones, R.H. (1993) for discussion on using AIC in this type of problems.

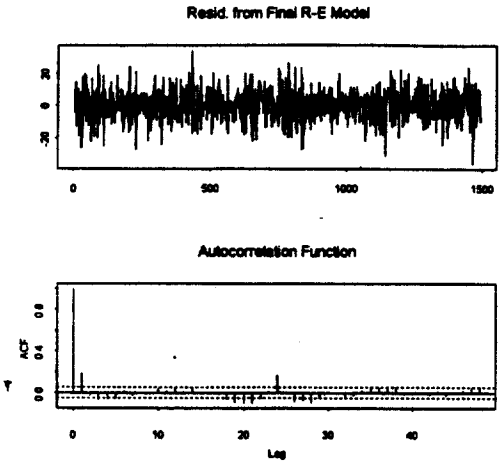

Figure 6 The sequential plot and autocorrelation function of the residuals from the final model (2).

The significant peaks at lag 1 and 24 in Figure 6 indicate that the residuals from the model (2) are still not ideal normals. We have tried other approaches, such as employing time dependent error distributions for e_{ijk}, but there are no improvements over the model (2). Those approaches, however, always gave the fixed-effects estimates that are consistent with that in the model (2). This reviewer thinks that with the limited sample size the model (2) is appropriate for DBP data. The estimates for the final model are given in Table 5.

Table 5 The estimates of fixed effects for the DBP data.

	Value	Std.Error	zratio
u_0	-2.46	1.77	-1.39
$u_{0.04}$	-8.11	2.03	-4.00
$u_{0.1}$	-16.86	1.77	-9.55
$u_{0.4}$	-24.23	2.40	-10.08
$u_{0.8}$	-20.94	2.20	-9.52
$\beta_{0.04}$	-0.13	0.04	-3.43
$\beta_{0.4}$	0.18	0.04	4.15
$\beta_{0.8}$	0.14	0.04	3.47

where $\beta_{0.1}$ is statistically non-significant and therefore eliminated from the final model.

8.2 The Models for SBP and HR Data Sets

The model (2) was also applied to the SBP and HR data sets. Table 6 presents the results

Table 6 The estimates of fixed effects for the SBP and HR data

	SBP				HR		
	Value	Std.Error	z ratio		Value	Std.Error	z ratio
u_0	-4.76	2.78	-1.71	u_0	-0.11	1.38	-0.08
$u_{0.04}$	-13.51	3.16	-4.28	$u_{0.04}$	3.79	1.38	2.76
$u_{0.1}$	-25.25	2.78	-9.08	$u_{0.1}$	8.57	1.58	5.41
$u_{0.4}$	-38.57	3.74	-10.31	$u_{0.4}$	13.84	1.87	7.39
$u_{0.8}$	-31.84	3.42	-9.30	$u_{0.8}$	23.46	1.72	13.68
$\beta_{0.04}$	-0.24	0.06	-4.06	$\beta_{0.1}$	-0.14	0.03	-4.84
$\beta_{0.4}$	0.41	0.07	5.86	$\beta_{0.4}$	-0.09	0.03	-2.62
$\beta_{0.8}$	0.19	0.06	2.94	$\beta_{0.8}$	-0.24	0.03	-7.76

Similar to the results for the DBP data, $\beta_{0.1}$ is statistically non-significant and eliminated from the final model for the SBP data. For the HR data, $\beta_{0.04}$ is statistically non-significant and similarly eliminated from the final model.

9. Conclusions

The p-values of log likelihood ratio tests for testing whether $u_0 = u_{0.04} = u_{0.1} = u_{0.4} = u_{0.8}$, or whether β_k's = 0 in the model (2) are given in the following table,

Table 7 P-values of comparison of treatment effect and tolerance.

H_0	P-values		
	DBP	SBP	HR
$u_0 = u_{0.04} = u_{0.1} = u_{0.4} = u_{0.8}$	<0.0001	<0.0001	<0.0001
β_k's = 0	<0.0001	<0.0001	<0.0001

We can conclude that the responses of fenoldopam patients are significantly different from that of placebo patients and the high dose groups have higher reductions in diastolic blood pressure and systolic blood pressure. There is a tolerance in high dose patients, the drug effect seems to be reduced over time.

The following table provides the estimation of the drug effects at time 1 hour, 24 hours and 48 hours based on the final model (2).

Table 8 Estimates of treatment effects $\hat{u}_k + \hat{\beta}_k t$ after 1, 24 and 48 hours.

Changes at		1 Hour	24 Hour	48 Hour
Diastolic Blood Pressure	0 ug/Kg/min	-2.46±1.77	-2.46±1.77	-2.46±1.77
	0.04 ug/Kg/min	-8.24±2.01	-11.13±1.77	-14.15±1.92
	0.1 ug/Kg/min	-16.86±1.77	-16.86±1.77	-16.86±1.77
	0.4 ug/Kg/min	-24.05±2.38	-19.87±2.10	-15.50±2.29
	0.8 ug/Kg/min	-20.80±2.18	-17.59±1.92	-14.25±2.09
Systolic Blood Pressure	0 ug/Kg/min	-4.76±2.78	-4.76± 2.78	-4.76± 2.78
	0.04 ug/Kg/min	-13.75±3.13	-19.19±2.78	-24.86±3.07
	0.1 ug/Kg/min	-25.25±2.78	-25.25±2.78	-25.25±2.78
	0.4 ug/Kg/min	-38.17±3.71	-28.81±3.30	-19.04±3.65
	0.8 ug/Kg/min	-31.65±3.39	-27.34±3.01	-22.84±3.34
Heart Rate	0 ug/Kg/min	-0.11±1.38	-0.11±1.38	-0.11±1.38
	0.04 ug/Kg/min	3.79±1.38	3.79±1.38	3.79±1.38
	0.1 ug/Kg/min	8.43±1.57	5.32±1.38	2.08±1.48
	0.4 ug/Kg/min	13.76±1.86	11.75±1.63	9.65 ±1.76
	0.8 ug/Kg/min	23.23±1.70	17.77±1.49	12.08±1.61

Concerned that the estimates at 1 hour and 48 hours might give extreme values, we also estimated the average changes of a blood pressure and heart rate at three time intervals: 1-16 hours, 17-32 hours, 33-48 hours. We fitted the data with the following piecewise saturated mixed-effects model:

$$Y_{ijk} = \begin{cases} u_1 + c_{1i} + e_{ijk}, & 0 < t_j <= 16.5, \\ u_2 + c_{2i} + e_{ijk}, & 16.5 < t_j <= 32.5, \\ u_3 + c_{3i} + e_{ijk} & 32.5 < t_j. \end{cases}$$

The estimates of u_1, u_2 and u_3 and their standard errors are given in the following table:

Table 9 Estimates of treatment effects during 1-16, 17-32 and 33-48 time periods.

Average changes during		1-16 Hours	17-32 hours	33-48 hours
Diastolic Blood Pressure	0 ug/Kg/min	-1.90±1.94	-1.90.±1.94	-1.90±1.94
	0.04 ug/Kg/min	-8.01±2.35	-11.82±2.01	-11.8±2.37
	0.1 ug/Kg/min	-13.71±2.35	-15.90±2.01	-16.53±2.37
	0.4 ug/Kg/min	-20.42±2.79	-18.21±2.38	-14.47±2.8
	0.8 ug/Kg/min	-20.29±2.55	-15.69±2.18	-16.56±2.56
Systolic Blood Pressure	0 ug/Kg/min	-5.29±3.06	-5.29±3.06	-5.29±3.06
	0.04 ug/Kg/min	-13.54±3.45	-19.60±3.18	-20.96±3.87
	0.1 ug/Kg/min	-25.13±3.45	-25.65±3.18	-26.14±3.87
	0.4 ug/Kg/min	-31.37±4.08	-27.18±3.76	-18.10±4.58
	0.8 ug/Kg/min	-33.19±3.73	-25.09±3.44	-27.92±4.19
Heart Rate	0 ug/Kg/min	1.78±1.38	1.78±1.38	1.78±1.38
	0.04 ug/Kg/min	5.18±2.30	3.71±1.44	4.53±1.63
	0.1 ug/Kg/min	10.22±2.30	5.15±1.44	4.51±1.63
	0.4 ug/Kg/min	14.31±2.72	11.58±1.71	10.90±1.93
	0.8 ug/Kg/min	25.15±2.48	15.56±1.56	16.20±1.76

From the Tables 8 and 9, we can conclud that although there is a tolerance, there are still substantial drug effects towards the end of 48 hours.

References:

Jones, R.H. (1993) *Longitidinal Data with Serial Correlation: A State-space Approach*, Chapman & Hall, London.

Laird, N.M and Ware, J.H. (1982) Random effects models for longitudinal data. *Biometrics*, **38**, 963-974.

Lindstrom, M.J. and Bates, D.M. (1988) Newton-Raphson and EM algorithms for linear mixed-effects models for repeated-measures data. *J. Am. Statist. Assoc.* **83**, 1014-1022.

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Arch. NDA 19-922

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APPLICATION NUMBER: NDA 19922

MICROBIOLOGY REVIEW(S)

JUN 26 1996

REVIEW FOR HFD-110
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 1 of CMC Presubmission of NDA 19-922
June 25, 1996

A. 1. **APPLICATION NUMBER:** 19-922

APPLICANT: Neurex Corporation
3760 Haven Avenue
Menlo Park, CA 94025

2. **PRODUCT NAMES:** fenoldopam mesylate (Corlopam injection).

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 10 mg/ml in 5 ml ampoules. Corlopam is to be administered by intravenous infusion.

4. **METHOD(S) OF STERILIZATION:** sterilization.

5. **PHARMACOLOGICAL CATEGORY:** Short-term treatment of hypertension when oral administration is not feasible or desirable and perioperative control of blood pressure.

B. 1. **DATE OF INITIAL SUBMISSION:** May 3, 1996

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** May 20, 1996

5. **DATE OF CONSULT REQUEST:** May 13, 1996

C. **REMARKS:**

The NDA was originally submitted by in December, 1988, and has since been withdrawn by the original sponsor. There were CMC deficiencies related to the manufacturing procedures. Neurex acquired the

rights to this product in 1994, and is resubmitting the NDA. The product submitted in the original NDA was a sterile solution manufactured by aseptic processing and packaged in glass vials. The proposed drug product is identical in formulation, packaged in 5 ml ampoules, and is .

D. CONCLUSIONS:

Corlopam injection is bactericidal and the prefiltration bioburden is therefore low. The bioburden is further reduced

The submission is recommended for approval on the basis of sterility assurance.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Brenda Uratani 6/25/96

Brenda Uratani, Ph.D.

6/24/96

cc:

NDA 19-922 CMC Presubmission
HFD-110 / Div. File
HFD-805 /Uratani
HFD-110/CSO/McDonald
drafted by: Brenda Uratani, 6/25/96
R/D initialed by P.Cooney, 6/25/96

APPEARS THIS WAY
ON ORIGINAL

MAR 21 1990

CONSULTATIVE REVIEW TO HFD-110
DIVISION OF MEDICAL IMAGING, SURGICAL AND DENTAL DRUG PRODUCTS

Microbiologist's Review No. 1
February 9, 1990

A. 1. NDA: 19-922 BI

APPLICANT:

2. PRODUCT NAME: Corlopam^{R} (fenoldopam mesylate)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Single dose vials with capacities of 2.5, 5.0 and 10ml containing 10 mg/ml fenoldopam for intravenous infusion with 0.9% NaCl injection or 5% dextrose injection.

4. METHOD(S) OF STERILIZATION: Aseptic Fill

5. PHARMACALOGICAL CATEGORY AND/OR PRINCIPLE INDICATION: Antihypertensive

6. DRUG PRIORITY CLASSIFICATION: 1C

B. 1. DATE OF INITIAL APPLICATION: December 12, 1988

2. DATE OF AMENDMENT(S): August 1, 1989 (subject of this review)

3. RELATED DOCUMENTS: Volume 1.1, December 12, 1988

4. ASSIGNED FOR REVIEW: August 11, 1989

C. REMARKS: The amendment was submitted to address concerns presented in a meeting on October 12, 1988 during which Dr. Cooney requested that the NDA describe microbiological control procedures at the manufacturing site and data regarding the preservative efficacy.

D. CONCLUSIONS: The application is not approvable for the subject drug.

David Hussong 3-21-90
David Hussong, Ph.D. PHC 3/21/90

cc:
Orig. NDA 19-922 BI
HFD-110
HFD-160/Consult File
drafted by: D.Hussong
R/D Init by: P.H.Cooney/02-12-90
F/T by: D.Flannigan/03-19-90
Wang #5562K