CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19922

MEDICAL REVIEW(S)

Medical Officer's Consultation Review of NDA 19-922 DEC - 5 1996
Ophthalmology

NDA 19-922 **Review date:** 12/3/96

Sponsor:

Drug: Fenoldopam

Pharmacologic Category: Post-synaptic dopamine-1 (DA-1) receptor agonist

Dosage Form and Route of Administration: IV Solution

Consult Request:

Included are the two study reports

- What is the significance of the IOP changes?
- Are such pressure increases likely or potentially capable of causing irreversible changes during infusion times of 24-48 hours?
- Will any premonitory symptoms be obvious prior to irreversible changes?
- Based on above, any labeling suggestions? i.e., 2nd line drug, tonometry prior to infusion?

Study 1: **Protocol 239**

Investigation of the Effect of Fenoldopam and Placebo on Intraocular Pressure in Patients with Elevated Intraocular Pressure (IOP)

Design: A randomized, double-masked, two period crossover study to compare the effects of a constant intravenous infusion of fenoldopam and placebo. 12 subjects with primary open angle glaucoma or intraocular hypertension with elevated IOP of 21 to 30 were enrolled. IOP was measured by pneumotonometry, other outcome measures included macular blood flow by blue field examination, visual field examination by automated perimetry and aqueous outflow facility measured by tonography and fluorophotometry. Patients would be terminated if IOP increased above 35 mmHg. Study medications were titrated to the highest tolerated of four dose levels (up to 0.5μg/kg/min) during a maximum infusion duration of 210 minutes on each of two study days.

Reviewer's Comments:

The study design has some problematic aspects. Pneumotonometry is not the most accurate measure of IOP. While it is a measure of IOP, the variability is greater (and the numerical values usually higher) than applanation tonometry. This is likely to make it more difficult to detect a difference between groups even if a difference exists. In addition, tonography may have an effect on IOP measurements.

There are currently no good methods to measure macular blood flow and the duration of the trial is too short to expect to see any visual field changes.

Results:

Thirteen subjects were enrolled. One subject was withdrawn on the first study day during placebo infusion following a corneal abrasion related to the tonography procedure.

Infusions were terminated in 5 subjects during dosing of fenoldopam and 1 subject during dosing of placebo because supine IOP rose to greater than 35 mmHg.

Mean IOP	Fenoldopam	Placebo
Baseline	29.2	28.4
15 min	29.5	27.7
35 min	30.5	27.8
55 min	32.3	27.8
75 min	33.5	28.0
90 min	33.8	27.8
105 min	33.8	28.6
150 min	34.3	29.9
180 min	33.6	29.8
210 min	31.9	29.1
225 min	31.5	29.6
240 min	29.4	29.0
270 min	26.6	27.4
330 min	25.1	26.5

Reviewer's Comments: *Assuming this trial was conducted during the day, IOP measurements would be expected to decrease during the study. Infusion of saline, could cause slight increases in IOP.*

The IOP measurements identified in this study represent a clear increase in the fenoldopam group compared to an expected baseline and compared to placebo.

Visual Field:

Change from Baseline	Fenoldopam	Placebo
Mean Sensitivity	-.28	-1.12
Mean Defect	0.33	1.12

Reviewer's Comments: *These changes are not meaningful, however the duration between tests is not adequate to expect any changes.*

Blue Field Exam

Change from Baseline	Fenoldopam	Placebo
Velocity	-0.07	0.02
Density	13.0	-11.4

Reviewer's Comments: *No significant changes.*

Tonography	Fenoldopam	Placebo
Change in Outflow	0.07	0.15

Reviewer's Comments: *No significant changes.*

Fluorophotometry	Fenoldopam	Placebo
Aqueous flow	0.19	0.24

Reviewer's Comments: *No significant changes.*

Study 2: **Protocol 088**

A Double-Masked, Placebo Controlled Crossover Study of the Effect of Intravenous Fenoldopam on Intraocular Pressure

Design: Randomized, double-masked, four period crossover study to compare the effects of a 2-hour intravenous infusion of fenoldopam. 13 healthy volunteers were enrolled. IOP was measured by a Perkins hand-held tonometer. Other outcome measures included tonography by Schiotz tonometer with a weighted plunger. Study medications included three dose levels (up to 1μg/kg/min).

Results:

IOP

Thirteen subjects were enrolled. One subject was withdrawn on the first study day prior to receiving medication because he was unable to tolerate the tonometric examination.

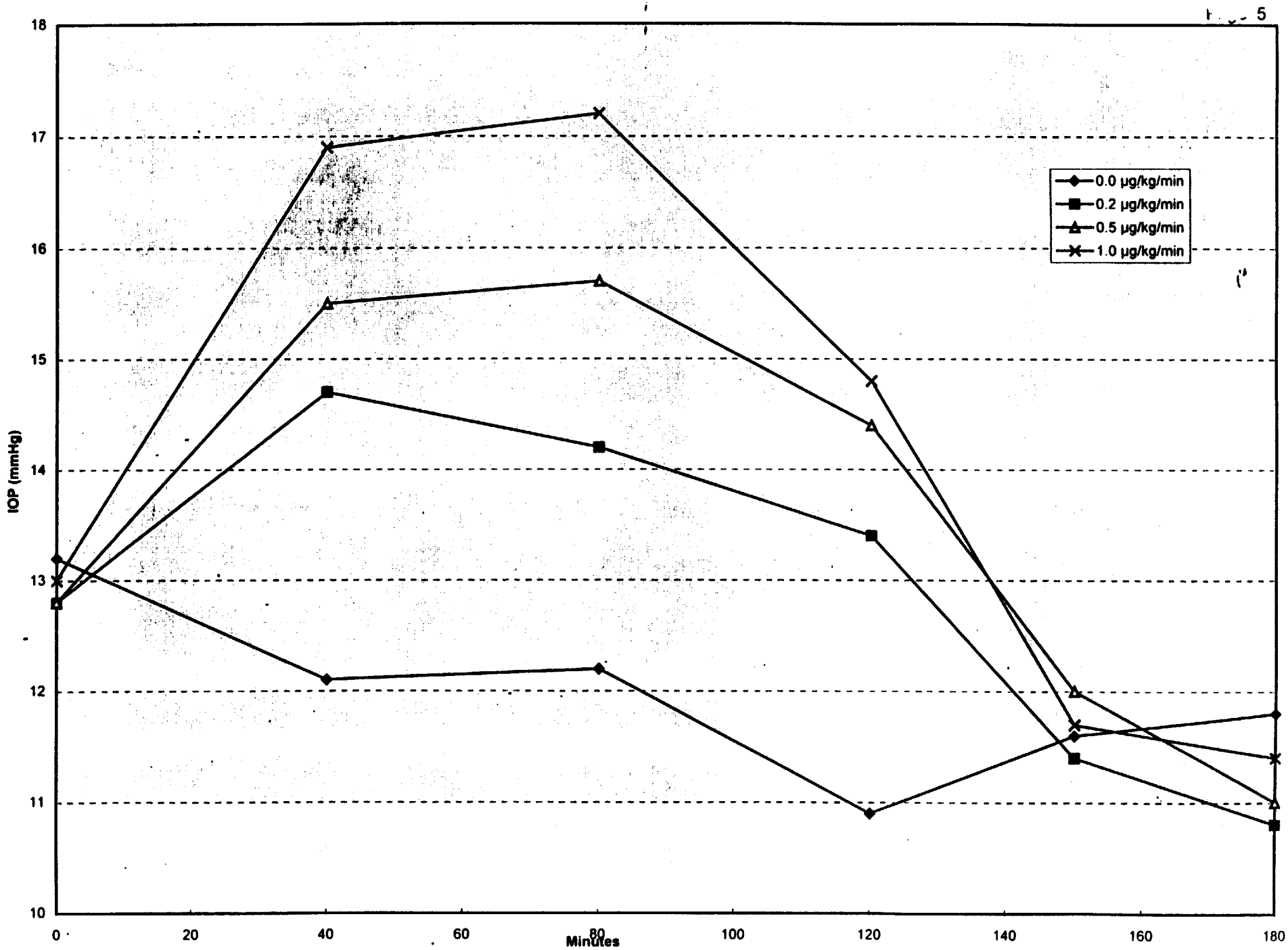
	Minutes of Infusion				End of Infusion	
	0	40	80	120	150	180
0.0 μg/kg/min	13.2	12.1	12.2	10.9	11.6	11.8
0.2 μg/kg/min	12.8	14.7	14.2	13.4	11.4	10.8
0.5 μg/kg/min	12.8	15.5	15.7	14.4	12	11
1.0 μg/kg/min	13	16.9	17.2	14.8	11.7	11.4

[see attached graph]

Aqueous Outflow

	Baseline		Final	
	P_0	C	P_0	C
0.0 μg/kg/min	13.6	.27	12.5	.30
0.2 μg/kg/min	14.1	.28	14.6	.21
0.5 μg/kg/min	13.9	.24	16.3	.18
1.0 μg/kg/min	13.6	.27	17.4	.20

P_0 = Estimated steady state intraocular pressure (mmHg)
C = Facility of aqueous outflow (μl/min/mmHg)


Study 088 - Fenoldop 0 minute infusion
IOP (mmHg)
Minutes
0.0 µg/kg/min
0.2 µg/kg/min
0.5 µg/kg/min
1.0 µg/kg/min
18
17
16
15
14
13
12
11
10
0
20
40
60
80
100
120
140
160
180

Reviewer's Comments: *The IOP measurements identified in this study represent a clear increase in the fenoldopam group compared to placebo. The outflow facility appears to be decreased in these patients.*

The amount of IOP increase exceeds the normal diurnal variation which occurs with IOP.

Summary:

1. It is not unexpected that a drug product which activates dopamine$_1$ (DA_1) receptors would cause an increase in intraocular pressure (IOP).

2. A clear dose response has been observed in patients treated with fenoldopam with respect to elevations in intraocular pressure. Individual IOP elevations were generally on the order of 2-8 mmHg, although occasionally were in the 10-12 mmHg range.

3. Mean IOP elevations of 4-6 mmHg may be clinically significant if the IOP remains elevated over a period of years. There is no evidence in the published literature which would support a safety problem in non-glaucoma patients with single day IOP elevations of up to 10 mmHg. Elevations of IOP at the level reported in these papers for less than a week's duration are highly unlikely to cause any permanent changes in normal individuals.

4. Elevations in IOP of the type noted in these studies may cause small permanent changes in the visual function of a subset of patients with glaucoma and ocular hypertension.

5. The IOP diurnal variation in normal individuals is usually much less than 5 mmHg (usually less than 3 mmHg). The IOP diurnal variation in glaucoma patients is often higher than normal individuals and may exceed 5 mmHg.

6. In the absence of IOP measurements (tonometry) on individual subjects, elevations in intraocular pressure are not usually detectable by a patient. The lack of reported events related to elevated intraocular pressure is no assurance that elevations have not occurred. The accurate measure of IOP requires an applanation tonometer. Accurate tonometers which are capable of measuring IOP in supine patients are not commonly available. The use of these tonometers usually requires an ophthalmologist or a technician trained in measuring IOP.

7. Demographic information including "iris color" and "family history of glaucoma" do not appear to have been collected and should have been.

Ophthalmology Consultant Recommendations:

1. The labeling of the product should include statements in the WARNINGS section which limit the use of this product in patients with a history of glaucoma or ocular hypertension, particularly those patients with visual field defects.

2. The labeling of the product should include statements which identify the drug products potential to elevate intraocular pressure generally in the range of 2-8 mmHg.

3. It is not practical and probably unnecessary to measure IOP in a clinical (non-study) setting prior to administration of the drug product. With the exception of extended use (i.e., greater than 1 week), it is probably unnecessary to monitor these patients (except those with ocular hypertension or glaucoma). If extended continuous therapy is anticipated, monitoring every 7-14 days is recommended.

Wiley A. Chambers, M.D.

cc: NDA 19-922
HFD-550/Consult File
HFD-550/Chambers

Medical Officer's Consultation of NDA 19-922
Ophthalmology

NDA 19-922
Consult

Submission date: 9/ 5/90
Consult request date: 10/ 1/90
Review date: 10/ 2/90

Sponsor:

Drug: Corlopam (fenoldopam mesylate) Infusion

Requested: Review of amendment.

Submitted: Published reports regarding increases in intraocular pressure (IOP) during fenoldopam mesylate infusion which occurred in a small number of normal volunteers and patients. The sponsor's submitted information has been summarized below.

1. Four published reports are enclosed. In both normal subjects and hypertensive patients, intraocular pressure was reported to rise an average of 3 and 4 mmHg, respectively. The normal diurnal variation of the parameter is 5 mmHg.

2. To date, no specific events related to elevated intraocular pressure have been reported in trials of intravenous fenoldopam. In 320 patients with severe hypertension enrolled in the intravenous fenoldopam trials, a total of two events of visual disturbances, on therapy, were noted.

3. Although intraocular pressure has only been studied in a small number of patients, the sponsor feels that a mild rise in IOP may occur in hypertensive patients receiving fenoldopam infusion. They also feel it unlikely that a rise of only 4 mmHg will be of significance to the majority of patients receiving fenoldopam. The following steps have been or will be taken by the sponsor:

   a. The sponsor has obtained the opinion of outside glaucoma expert.

      i. The sponsor's consultant has reviewed the articles and does not consider the IOP elevation associated with the use of fenoldopam infusion to be clinically significant because of the small magnitude of the increase and the short duration of the elevation.

      ii. The consultant has recommended that until further study of IOP elevation is undertaken, patients with a history of glaucoma be excluded from clinical trials due to the unknown risk for that patient population.

   b. The ongoing protocols have been amended to exclude patients with a history of glaucoma.

   c. The sponsor is working their consultant to design trials to appropriately study the change in intraocular pressure.

DCRDP Medical Officer's Recommendations

1. The cases cited are from published reports. It is unknown how many additional cases have been reported to the respective regulatory agencies. An update of safety reports should be requested.

2. The sponsor should be requested to obtain IOP measurements in all patients in all studies.

Ophthalmology Consultant's Comments:

1. *It is not unexpected that a drug product which activates dopamine$_1$ (DA_1) receptors would cause an increase in Intraocular Pressure (IOP).*

2. *The sponsor reports the increases in IOP as average rises in IOP (4 mmHg). It would be more appropriate to also report the range of increases. In the published papers, it appears that IOP increases were observed in almost all patients examined (2-6 mmHg). There may be genetic factors which influence the amount of IOP elevation.*

3. *Mean IOP elevations of 4-6 mmHg may be clinically significant if the IOP remains elevated over a period of years. There is no evidence in the published literature which would support a safety problem in non-glaucoma patients with single day IOP elevations of up to 10 mmHg. Elevations of IOP at the level reported in these papers for less than a week's duration are highly unlikely to cause any permanent changes.*

4. *The IOP diurnal variation in normal individuals is usually much less than 5 mmHg (usually less than 3 mmHg). The IOP diurnal variation in glaucoma patients is often higher than normal individuals and may exceed 5 mmHg.*

5. *I agree with the sponsor's consultant that the studies performed in normals cannot be used to predict the effect in patients with glaucoma. The studies also cannot be used to predict the effect in patients with ocular hypertension. Until patients with ocular hypertension and patients with glaucoma are specifically studied, they probably should be excluded from the current protocols.*

6. *In the absence of IOP measurements (tonometry) on individual subjects, elevations in ocular pressure are not usually detectable by a patient until optic nerve damage has occurred. The lack of reported events related to elevated intraocular pressure is no assurance that elevations have not occurred.*

7. *The accurate measure of IOP requires an applanation tonometer. Accurate tonometers which are capable of measuring IOP in <u>supine</u> patients are not commonly available. The use of these tonometers usually requires an ophthalmologist or a technician trained in measuring IOP. Ideally, it would be desirable to measure the IOP in all patients currently enrolled in all clinical protocols. As a practical matter, the inclusion of IOP measurements in all studies may not be possible.*

8. *It would also be advantageous to have the sponsor conduct studies which specifically examine these IOP elevations. In such studies, demographic information including "iris color" and "family history of glaucoma" should be collected.*

Ophthalmology Consultant Medical Officer's Recommendations:

1. Ongoing protocols should exclude patients with ocular hypertension or glaucoma.

2. The sponsor should conduct clinical trials to more completely study the IOP elevation potential of fenoldopam mesylate.

Wiley A. Chambers, M.D.

cc: NDA 19-922
HFD-110
HFD-111/Roeder
HFD-110/Graham
HFD-520/Chambers

10/4/90

101

MAR 3 1992

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA Number: 19-922
Drug Name: Fenoldopam
Sponsor:

Submission Date: February 10, 1992
Submission Type: NDA, Clinical Protocol
Date of Receipt: February 18, 1992
Review Complete: February 26, 1992

Content: Clinical report protocol D 1101

Background: Additional clinical protocol to evaluate efficacy of fenoldopam in patients with severe hypertension.

Review: The submision was reviewed. Fenolodpam (F) was compared to sodium nitroprussside (SN) in the treatment of severe hypertensives (DBP > 120 mm Hg). This was an open label study with three phases - up-titration, maintenance and down-titration. Patients were observed for 48 hours post-treatment. Investigators rated response as success or failure. A response could be rated as "success" even if the desired reduction in pressure was not achieved. Concomitant antihypertensives were permitted after initial maintenance period. All these factors complicate interpretation of data and there is a possibility of bias in interpretation of open label data.

Recommendations:
1 Fenoldopam appears to reduce DBP to the same extent as does SN in severe hypertensives. However, due to the confounding factors of concomitant antihypertensive agents and investigator interpretation, it is difficult to evaluate F's actual effect
2 It is difficult to ascertain the duration of effect, as additional agents were added
3 Subgroup analyses should be performed, as stated in overall summary

Signature:

BZ Friedman

cc:
Original NDA
HFD-110/Division File
HFD-110/CSO

A MULTINATIONAL, MULTICENTER, OPEN LABEL COMPARISON OF IV "CORLOPAM" VERSUS SODIUM NITROPRUSSIDE IN PATIENTS WITH SEVERE HYPERTENSION

PROTOCOL 8256/D1101/WW

SUMMARY

Investigators: Study conducted in 24 centers in 5 countries

Design:

Open label, randomized, dose-titration trial in severe hypertensives (DBP > 120 mm Hg), requiring immediate parenteral treatment. Patients received either fenoldopam (F) or sodium nitroprusside (SN) IV.

Prior to initiation of treatment, eligible patients had all their antihypertensives withdrawn and underwent baseline tests and procedures. They were then randomized to continous infusion of F or SN on a 1:1 basis. The infusions consisted of an up-titration phase to reach protocol specified DP reductions. This was followed by 6-18 hour maintenance, 2 hour down-titration and 48 hour post-infusion phases. Maximum duration of infusion was not to exceed 24 hours.

Initial doses were 0.1 mcg/kg/min (F) or 0.5 mcg/kg/min (SN). [Note, that in future, doses will be stated without the units mcg/kg/min]. These initial doses were up-titrated to reduce DBP to either: < 110 mm Hg, if initial DBP was 120-150 mm Hg, or by at least 40 mm Hg if initial DBP was 150-170 mm Hg, or less of a reduction if the investigator thought that further reduction would be unsafe. After achieving the required reduction, dosing was kept constant for first 30 minutes of maintenance period. Thereafter, dosing was to be constant but could be altered to maintain DBP reduction for up to 18 hours maintenance dosing. Infusion rate was then down-titrated over 2 hours. Antihypertensive agents could be added at beginning of down-titration and continued through post-infusion phase, if necessary. All vital signs were measured at regular intervals. Based on reductions in DBP, investigators judged the study medication as successful, partial successful or treatment failure.

Demography

A total of 183 patients (96 males and 87 females, age range 22 to 80 years) were enrolled and randomized to F (90) or SN (93). Demographics were similar in both groups.

Concomitant Medications

During up-titration, severe CHF patients could receive two doses furosemide parenterally (20-40 mg) at least one hour apart. Other diuretics or antihypertensives were not permitted during up-titration or maintenance phases, but were allowed during down titration and follow up phases. In F group 51/90 (57%) received antihypertensives compared to 57/93 (61%) SN group.

Withdrawals from Study

There were 37 early withdrawals, 19 F and 18 SN. Of these, 10 F and 12 SN withdrew due to clinical events and 6 F and 3 SN for insufficient therapeutic effect. In addition 3 in each group withdrew due to patient perceived sufficient effect.

Efficacy Results

There were 153 (75 F and 78 SN) accepted for efficacy evaluation. Baseline characteristics were similar. Both groups produced "high overall success rates" in reducing DBP; F had 99% success rate and SN 91%. The differences were not statistically significantly different. Both drugs "produced rapid and comparable lowering of diastolic blood pressure during uptitration which was dose related." Time to complete uptitration was similar (F 85 minutes) and SN (94 minutes). At beginning of maintenance, average DBP decrease for both drugs was 29 mm Hg. After 30 minutes constant infusion rate, decreases were 30 mm Hg (F) and 31 mm Hg (SN). These decreases were maintained at 6 hour time point, and for 12 hours in some patients. Increases in heart rate was ± 7 bpm. SBP was reduced significantly, more with SN than with F. There was no evidence of tolerance to DBP in either group. Average maintenance doses were 0.41 (F) and 1.67 (SN).

During down-titration, average DBP decreases were maintained in both patients receiving concomitant antihypertensives and in those not receiving concomitant medications. During post-infusion phase > 90% in both groups received additional antihypertensives. Reductions in DBP were maintained during this period.

Safety

No deaths occurred during study or follow up period. Withdrawals for adverse events (AEs) were similar, (F 11% and SN 13%). On-therapy events occurred in 56% F and 53% SN patients, and in 48 hour post-treatment phase, it was 31% F and 31% SN. Most AEs were associated with cardiovascular system (flushing, hypotension and decreased blood pressure). Most frequent on-therapy AE was headache. The number of severe events were 5 F and 4 SN.

There were no clinically important differences in laboratory values for either group. More F patients (5) had low serum potassium than SN (1). There were no clinically important ECG changes with either group.

Conclusions

Sponsor concludes that F was as effective as SN in reducing DBP in severely hypertensive patients requiring immediate parenteral antihypertensive therapy. Safety profiles are also similar.

MEDICAL REPORT

Objective

To evaluate and compare the efficacy and safety of IV fenoldopam (F) and sodium nitroprusside (SN) in reducing blood pressure in patients with severe hypertension requiring immediate parenteral treatment. Safety was to be evaluated and compared during infusion period and for 48 hours post-infusion.

Investigators

The study was conducted in 24 centers in 5 countries. A list of investigators is attached.

Dates of Study

Date of initiation	12 December 1988
Date of completion	2 January 1990
Date of report	October 1991

Design

Open label, multinational, multicenter, randomized comparison of efficacy and safety of F and SN.

Patient Selection

Inclusion

1 Men and women, ages 21-80 years with severe hypertension (DBP 120 mm Hg or more) requiring immediate blood pressure reduction with parenteral administration of medication.

Exclusion

1 Pregnant or lactating patients
2 DBP < 120 mm Hg
3 Pheochromocytoma or history of malignant uncontrolled ventricular arrhythmias
4 Known history of thrombocytopenia (<125,000/mm ^{3})
5 Chronic hemodialysis or peritoneal dialysis
6 Transplant patients receiving immunomodulators
7 Dopamine agonists, phenothiazines or dopamine antagonists within 12 hours of infusion
8 Parenteral analgesics within 6 hours of initiation of infusion
9 Investigational drugs within previous 30 days
10 Hypersensitivity to F or SN

Procedures

Prior to initiation of therapy, baseline tests and procedures were performed and patients randomized to F or SN. Patients were hospitalized through course of therapy and for at least 48 hours post-infusion. Administration of drug was divided into three phases:

Protocol D-1101

Appendix 1.1
List of Investigators and Patient Distribution by Investigators

Center Number	Investigator	Total Number of Patients
010	Dr. Richard Byyny Univ. of Colorado Health Science Division of Internal Medicine Denver, CO 80262	1
002	Dr.Donna Craig Atlanta Medical Associates 3250 Howell Mill Road, NW Atlanta, GA 30327	7
034	Dr. P. Deleeuw Zuiderziekenhuis Groene Hilledijk 315 Rotterdam 3075 EA Netherlands	5
029	Dr. Jacobus De Vaal University of the Orange Free State Department of Critical Care Bloemfontein 9300 Zaire	9
020	Dr. Lala Mathers Dunbar CRO-PFDA: Pharmaceut. Food & Drug c/o Jeffrey Gardner Roslyn Heights, NY 11577	32

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Appendix 1.1
List of Investigators and Patient Distribution by Investigators

Center Number	Investigator	Total Number of Patients
005	Dr. William Elliott University of Chicago Department of Medicine 951 E. 58th Street Chicago, IL 60637	12
003	Dr. George Emmanuel Bay Pines V.A.M.C. 3rd Floor, Room 111A Bay Pines, FL 33504	2
016	Dr. G. Foulke UC Davis Medical Center 2315 Stockton Blvd., trailer Sacramento, CA 95817	3
021	Dr. Alan Gelb San Francisco General Hospital 1001 Poterro Avenue San Francisco, CA 94110	3
017	Dr. Francisco Gonzales LSU School of Medicine Univ. Medical Center - Head SE New Orleans, LA 70112-282	12

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List of Investigators and Patient Distribution by Investigators

Center Number	Investigator	Total Number of Patients
009	Dr. Virginia Hammond St. Joseph's Heart Institute 3001 W. Buffalo Avenue Tampa, FL 33677	13
032	Dr. Gerhart Hitzenberger I. Med. Klinik der Universitaet Lazarettgasse 14 Wien A-1090 AT	9
033	Dr. Guenther Krejs I. Med. Klinik der Universitaet Auenbruggerplatz 15 Graz A-8036 AT	11
008	Dr. M. Andrew Levitt Emergency Medicine 293 Thompson Bldg. Philadelphia, PA 19107	4
031	Dr. Gaetano Lotti Universita Degli Studi Viale Benedetto 15, 10 Genova, Italy 16145	6
015	Dr. Lionel Mailloux North Shore University Hospital Division of Nephrology & Hypertension Manhasset, NY 11030	6

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List of Investigators and Patient Distribution by Investigators

Center Number	Investigator	Total Number of Patients
001	Dr. William Miller Coordinated Hypertension Associates Division of Nephrology Wilmington, DE 19806	1
011	Dr. Allan Niederman Broward General Medical Center Ft. Lauderdale, FL 33308	7
012	Dr. Edward Panacek University Hospitals of Cleveland 2074 Abington Rd. Cleveland, OH 44106	12
014	Dr. Kodanjudi Ramanathan University of Tennessee Medical Center 951 Court Avenue Memphis, TN 38163	9
007	Dr. Michael Rudnick The Graduate Hospital Nephrology Division Philadelphia, PA 19146	6
030	Dr. Allessandro Salvadeo Clinica del Lavoro Via Boezio 24 Pavia 27100, Italy	11

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List of Investigators and Patient Distribution by Investigators

Center Number	Investigator	Total Number of Patients
013	Dr. Peter Schulman University of Connecticut Health Science Center Cardiology L2108 Farmington, CT	1
019	Dr. Lawrence Weisberg Cooper Hospital/University Med Department of Medicine Camden, NJ 08103	1

1 Up-titration (Phase 1): DBP was to be reduced to < 110 mm Hg if initial DBP was 120-150 mm Hg, or by at least 40 mm Hg if initial DBP was > 150 mm Hg, or less than these amounts if the investigator thought further acute reduction may be unsafe for the patient. This period was 4-16 hours duration.

2 Maintenance period (Phase 2): When protocol specified reductions in DBP had been achieved, infusion was to be maintained for at least 6 hours and not more than 18 hours; total infusion time could not exceed 24 hours. If, after initial 30 minutes, DBP increased during maintenance, infusion was to be up-titrated as previously defined.

3 Down-titration: This took place over 2 hours and infusion was then terminated. Antihypertensives and/or concomitant medications could be given during down-titration.

Patients were evaluated for at least 48 hours post-infusion with follow up assessments at 7-10 days after study termination.

Doses

Both drugs were administered by infusion pump for up to 24 hours. Initial rate of infusion was 0.1 mcg/kg/min F or 0.5 mcg/kg/min SN. (In the rest of this report, units mcg/kg/min will be omitted). Dose was increased no more often than very 10 minutes with maximum increments of 0.1 for F and 1.0 SN. Maximum infusion rate was 1.6 F and 8.0 SN. Decreases in dose were permitted 3 times, separated by 10 minute intervals.

Treatment Phase

Eligible patients were randomised to their respective treatment either in the emergency room or in ICU. All antihypertensives were withdrawn before initiation of treatment. Maximum infusion time permitted was 24 hours and further infusion was not allowed.

During up-titration period, F or SN was given until specified reductions in DBP were obtained. Vital signs were recorded 10 minutes after any change in dose. DBP was not to fall below 95 mm Hg. If this occurred, infusion rate was to be decreased or terminated. Up-titration was not to exceed 16 hours, to allow 6 hours maintenance and 2 hour down-titration.

When desired DBP was attained, infusion rate was maintained for 6 hours and vital signs measured every 10 minutes for initial 30 minutes, every 15 minutes for one-and-a -half hours, then every 30 minutes for 4 hours, then hourly. Infusion rate was gradualy decreased during down-titration phase over a period of 2 hours. Dose was decreased to 50% of maintenance dose. After an additional hour, infusion was stopped. Vital signs recorded prior to dose reduction and every 10 minutes after dose decrease.

During post-infusion phase, patients could receive additional antihypertensives and were monitored in hospital for 48 hours. Vital signs recorded at 5, 10, 15, 20, 25, 30, 45 and 60 minutes, every hour for 3 hours, every 2 hours for 8 hours, then daily for 36 hours.

Efficacy Assessments

Eficacy was assessed by change in DBP during maintenance phase and by investigators' evaluation of response, classified as follows:

Treatment success: At end of 6 hour maintenance, there was (i) reduction in DBP to < 110 mm Hg, if initial DBP was 120-150 mm Hg, or reduction of at least 40 mm Hg, if baseline DBP was > 150 mm Hg or (ii) less than these values if the investigator thought it unsafe to decrease pressure further.

Partial success: This was reported if investigator thought a satisfactory reduction in DBP had been obtained, but less than that defined above.

Treatment failure: This was reported if, within 16 hours of initiation of infusion, there was an inadequate response, and infusion was terminated with addition of other antihypertensive therapy; or termination due to drug related adverse events.

Safety Monitoring

Lab tests were done at screening, during infusion and post treatment. Funduscopic exams, ECGs and vital signs were recorded at screening and during maintenance and post-treatment phase.

Protocol Amendments

Exclusion criteria

Preeclamtic and eclamptic women; use of dopamine agonists etc, at start of infusion, rather than within 12 hours; Significant surgical procedures within previous 7 days.

Additional significant amendments were: (i) If DBP decreased below 95 mm Hg, dose could be reduced three times, at 10 minute intervals; if DBP was still below 95 mm Hg after this time, infusion was terminated. (ii) During first 30 minutes of maintenance, no dose adjustment was allowed. After 30 minutes, dose could be increased or decreased, if necessary. (iii) During post-treatment, vital signs were recorded at 5, 10, 15, 20, 25, 30, 45 and 60 minutes and then hourly for 3 hours and then every 2 hours for 8 hours. (iv) Primary efficacy index was changed from difference between baseline and hour 6 of maintenance to difference between baseline and the half-hour reading of maintenance. Change at hour 6 was now a secondary index. Hour one is also a secondary index.

Variations from Protocol

The following were protocol variations:

a. Two preeclamtic patients were accepted for efficacy
b. Two patients with thrombocytopenia were accepted
c. One patient received antihypertensive drugs during up-titration and maintenance; excluded from analysis for another violation

d. Two patients were infused for > 24 hours. One was excluded for another violation
e. Maintenance was < 6 hours for 32 patients. Three had maintenace > 18 hours. None were excluded from analysis.
f. Vital signs were to be obtained 10 minutes after and immediately prior to dose change. This was not done for 93 patients.
g. DBP < 95 mm Hg (with conditions) were to be withdrawn; 114 patients were not withdrawn

Demography

A total of 183 patients (96 males, 87 females) were enrolled in 24 centers. There were 90 F and 93 SN randomized. Demographics were similar in both groups. (From sponsor Table 1)

Demographic Characteristics

	Fenoldopam		Nitroprusside	
Males	47	52%	49	53%
Females	43	48%	44	47%
Age				
20-39	27	30%	26	28%
40-59	47	53%	47	51%
60-80	15	16%	20	21%
> 80	1	1%	0	0%
Mean age	46.9 ± 1.3		48.1 ± 1.2	
Range	22-80		22-74	
Weight (mean, kg)	80.7 ± 1.9		80.6 ± 2.4	
American Indian	0		1	1%
Black	57	63%	59	63%
Caucasian	33	37%	30	32%
Melanesian	0		1	1%
Oriental	0		2	2%

Review of patients by country showed a similar distribution for both treatments. There were 11% per group from Austria, 2-3% Holland, 10-9% Italy, 4-5% S. Africa and 72% USA.

Medical History

All had acute hypertensive episodes. All, but one, had been diagnosed with pre-existent hypertension. For F, the average baseline values were 213/136 mm Hg and 87 bpm. The values for SN were 210/133 mm Hg and 84 bpm. Average durations of hypertension were 11 years 6 months (F), range 1-38 years and 9 years 5 months (SN), range 1 day to 36 years 7 months. Second most common condition was cardiomegaly (F 14%, SN 19%) and CHF (F 11%, SN 6%).

Prior antihypertensive therapy was received by 57% F and 61% SN patients. The types of drugs were similar in both groups. During down-titration, 63% in both groups received concomitant antihypertensives.

Dosing Distribution

Duration of F infusion ranged from 0.9 hours to 28.3 hours (mean 9.5, median 9.2 hours). Majority (69%) received infusion for 6-12 hours. The duration for SN 0.5 to 30.7 hours (mean 9.3, median 8.5 hours); 72% were from 6-12 hours. Appendix 6.1 (reference cited) gives the following numbers:

	F	SN
Mean duration	9.28	9.19
Median	9.01	8.51
Minimum	0.55	0.33
Maximum	28.16	30.44

Maximum rates of infusion were 0.1 to 2.9 (average 0.61) F with 51% having infusion rates 0.1 to 0.39; 21% 0.4 to 0.69 and 16% > 1.5. For SN, the maximum rates were 0.39 to 8.0 (average 1.81). Of these 25% were 0.5 to 0.99, 42% 1.5 to 3.49 and one patient had a rate > 7.5.

Cumulative doses F ranged from 0.45 to 131.69 mg (average 19.1); 36% received 2.5 - 10 mg, 32% 10-30 mg. SN cumulative dose range was 1.49 to 423.97 mg, average 58.33 mg. 44% received between 10 and 50 mg and 22% 50 to 100 mg.

Withdrawal from Study.

Of 183 enrolled, 19 F and 18 SN were withdrawn for the following reasons: 10 F and 12 SN for AEs; 6 F and 3 SN for insufficient response; 3 each for sufficient response.

Results - Efficacy

Of 183 enrolled, 153 were evaluable for efficacy, 75 F and 78 SN. The reasons for patient exclusions were (extracted from sponsor Table 4).

Reasons	F	SN
No maintenance phase	7	3
Maintenance dose changed < 25 minutes	2	5
Interval between dose change < 10 minutes (up)	3	1
BP device changed	0	3
Interval between dose change < 10 minutes (maintenance)	0	2
Duration maintenance < 25 minutes	0	1
Prohibited medicines < 12 hrs prior to start	1	0
Study med discontinued > once	1	0
Prohibited meds during infusion	1	0
TOTAL	15	15

Of the evaluable patients, there were 37 males and 38 females (F) and 42 males and 36 females SN. The mean respective ages were similar to overall group. Baseline DBPs were 135 mm Hg F and 133 mm Hg SN. In F group, there were 64 with DBP 120-150 and 11 > 150 mm Hg. The respective numbers for SN were 75 and 3.

Change in DBP from Baseline

These data are taken from sponsor Appendices 7.SA.1A., 7.SA.1B and 7 SA.3. No discussion of these data is in the text of the report to this point. It may occur later, but as these are the next Appendices in sequence, it was decided to include the data now.

DBP Baseline and Change from Baseline During Maintenance

Time	N	Fenoldopam	N	Nitroprusside
Per Protocol - No Centers Deleted				
Baseline	75	135	78	133
Start Maintenance	66	- 30	71	- 29
½ Hour	73	- 30	73	- 31
1 Hour	72	- 32	74	- 34
6 Hour	58	- 29	64	- 32
End Maintenance	38	- 30	46	- 31
Per Protocol - Centers Deleted				
Baseline	68	136	68	133
Start Maintenance	61	- 30	62	- 29
½ Hour	68	- 30	65	- 31
1 Hour	65	- 29	64	- 31
6 Hour	53	- 30	57	- 32
End Maintenance	34	- 31	39	- 31
Per Protocol - Intent-to-Treat				
Baseline	83	136	90	132
Start Maintenance	74	- 30	83	- 29
½ Hour	80	- 30	84	- 31
1 Hour	81	- 33	87	- 34
6 Hour	69	- 28	72	- 31
End Maintenance	53	- 28	50	- 29

Overall Success Rate

Investigator determined response of success was recorded in 70 F (93%) and 69 SN (88%) patients and partial success in 5% and 3%, respectively. (It must be remembered that (i) this is an open label study; (ii) investigator could determine a success even though the required decrease in DBP was not

achieved. This could, in reviewer's opinion, lead to bias in interpretation). One (2%) F and 7 (9%) SN were determined to be treatment failures. This difference approached, but did not reach statistical significance. (To put everything in perspective, it must be remembered that 6 F were withdrawn due to lack of efficacy compared to 3 SN. If these are added to treatment failures, the numbers would be 7 F and 10 SN, not too much different).

Of 57 F with baseline DBP < 150 mm Hg, 55 (96%) achieved maintenance control of < 110 mm Hg. Of 68 SN, 60 (88%) were controlled. Ten of eleven F (91%) with DBP > 150 mm Hg at baseline were judged successes compared to 3/3 (100%) SN. The partial successes had decreases in DBP of 28, 22, 40 and 3 mm Hg with F and 31 and 33 mm Hg with SN. This patient had, apparantly, responded at end of up-titration with 31 mm Hg reduction, classified as partial success, and then DBP increased by end of infusion.

Success by Maintenance Dose

This dose was one which adequately controlled DBP as per protocol specifications. Majority of F (37/70, 53%) who successfully responded were maintained on 0.1-0.39 dose.

Success Rate by Maintenance Infusion Rate (sponsor Table 6)

Maintenance Rate	Success		Partial	
Fenoldopam				
< 0.1	14	20%	0	0%
0.1 - 0.39	37	53%	1	25%
0.4 - 0.69	10	14%	0	0%
0.7 - 0.99	6	9%	1	25%
1.0 - 1.39	1	1%	0	0%
> 1.39	2	3%	2	50%
Nitroprusside				
< 0.5	7	7%	0	0%
0.5 - 0.99	19	28%	1	50%
1.0 - 1.49	13	19%	0	0%
1.5 - 3.49	24	35%	1	50%
3.5 - 5.49	5	7%	0	0%
> 5.49	3	4%	0	0%

Change from Baseline in DBP by Titration Dose

Average decrease in DBP at each dose was evaluated (sponsor Table 7). There were dose related decreases for both F and SN. For F, the decreases ranged from 9 mm Hg (0.10) to 39 mm Hg (1.00). (N= number observations)

Average Decrease DBP from Baseline (Selected Doses)

		Fenoldopam			SN		
Dose	N	Baseline	Decrease	Dose	N	Baseline	Decrease
0.1	168	137	9	0.50	214	133	12
0.2	102	137	18	0.75	20	138	22
0.5	23	138	20	2.0	44	140	26
0.7	13	144	29	3.0	29	149	19
0.9	9	147	27	4.0	12	148	33
1.0	12	146	39	.....			

Blood Pressure and Heart Rate During Maintenance

Sponsor Table 8 summarizes effects of the two treatments from completion of up-titration to end of maintenance. Mean decrease in DBP at beginning of maintenance was 29 mm Hg for both groups. Reductions in SBP were 33 mm Hg F and 39 mm Hg SN.

Average Change in DBP During Maintenance

Time (Hr)	N	Fenoldopam	N	Nitroprusside
Baseline	75	135	78	133
Start Main.	66	- 29	71	- 29
0.5	73	- 30	73	- 31
1.0	72	- 29	75	- 32
6.0	58	- 29	64	- 33
End	38	- 29	46	- 31

The reductions in SBP were similar for both groups, 33 mm Hg F and 39 mm Hg SN. Changes in heart rate were 5 and 4 bpm, respectively.

Changes in Vital Signs at Half, One and Six Hours and End of Maintenance

Reductions in SBP with SN (44 mm Hg) were significantly greater than F (36 mm Hg) from half hour until end of 6 hour period. Heart rate increased by 7 bpm with F and by 6 bpm with SN.

The one and six hour recordings are summarized in the next Table (from sponsor Table 9).

Average Change from Baseline in SBP and HR

	Fenoldopam			Nitroprusside	
Time	N	SBP	HR	N	SBP	HR
Baseline	75	212	87	78	210	84
Start Main	66	- 33	5	71	- 39	4
0.5 hr	73	- 36	7	73	- 44	6
1 hr	72	- 34	6	74	- 45	5
6 hrs	58	- 39	3	64	- 44	2
End	38	- 29	2	45	- 42	4

For infusion > 12 hours, sponsor states that DBP "continued to remain below baseline at levels comparable to that seen at one and six hour time points for both fenoldopam and nitroprusside". For F, the one and 6 hour decreases were 29 mm Hg. However, in sponsor Table 10, the decrease for 12 hours is given as 45 mm Hg, with similar reduction for SN. Sponsor was contacted, as it was difficult to identify the 9 F patients treated for > 12 hours. Sponsor has replied that their 12 hours is actually ± 2 hours, i.e., 10 hours or more. (As in original NDA, this submission is not exactly reader friendly, with Appendices and data not following sequentially, resulting in time consuming search for data).

Average Time to Maintenance

Average time to maintenance and average maintenance dose are summarized in sponsor Table 11. Average time to maintenance was 1 hour 25 minutes (F) and 1 hour 34 minutes SN. The respective doses at start and end of maintenance were 0.38 and 0.41 F, and 1.61 and 1.67 SN.

Frequency of dose increases during maintenance was higher in F group, while frequency of dose decreases was higher for SN.

Patients with Dose Changes During Maintenance Period

	Evaluable				Intent-to-Treat			
Category	F		SN		F		SN	
Increase	10	13%	5	6%	9	11%	6	7%
No change	28	37%	25	32%	26	31%	25	28%
Decrease	23	31%	35	45%	27	33%	44	49%
Incease/decrease	14	19%	13	17%	21	25%	15	17%

Blood Pressure During Down Titration

DBP during down titration in patients not receiving additional antihypertensives was similar in both groups. (Sponsor Table 13)

DBP During Down-Titration - Patients Not Receiving Antihypertensives

	N	Mean (F)	N	Mean (SN)
Baseline	24	135	33	133
Down Titration				
Start	24	110	33	112
1 Hour	22	112	33	112
2 Hour	23	111	33	108
End	24	102	33	101

The corresponding data for patients receiving concomitant antihypertensives are shown in the next Table. The decreases for F are greater than those seen in the above group, while the decreases with SN are similar to the group not receiving concomitant therapy.

DBP During Down-Titration - Patients Receiving Antihypertensives

	N	Mean (F)	N	Mean (SN)
Baseline	28	136	30	134
Down Titration				
Start	27	107	30	105
1 Hour	28	101	29	107
2 Hour	24	95	26	106
End	24	96	30	105

The decreases in DBP were essentially the same, irrespective of the number of antihypertensive agents used.

DBP During Post-Infusion Phase

The following Table summarizes DBP during post-infusion phase, irrespective of addition of other antihypertensives or not.

DBP Post-Infusion Phase

Time	N	F	N	SN
Baseline	70	136	76	134
End Infusion	69	101	76	101
1 hour	66	104	73	106
2 hours	56	107	68	106
4 hours	48	106	64	107
6 hours	39	108	57	106
8 hours	39	104	52	103
End	70	97	76	97

The most commonly used antihypertensives were arteriolar smooth muscle relaxants, calcium channel blockers, ACE inhibitors, central and peripheral acting antiadrenergics, beta blockers and diuretics.

SAFETY

All patients (N = 183) who received at least one dose of drug were evaluated for safety; 90 F and 93 SN.

There were no deaths reported during the study.

Withdrawal for AEs

Ten (11%) F and 12 (13%) SN were withdrawn due to AEs.

DBP During Down-Titration - Patients Receiving Antihypertensives

	N	Mean (F)	N	Mean (SN)
Baseline	28	136	30	134
Down Titration				
Start	27	107	30	105
1 Hour	28	101	29	107
2 Hour	24	95	26	106
End	24	96	30	105

The decreases in DBP were essentially the same, irrespective of the number of antihypertensive agents used.

DBP During Post-Infusion Phase

The following Table summarizes DBP during post-infusion phase, irrespective of addition of other antihypertensives or not.

DBP Post-Infusion Phase

Time	N	F	N	SN
Baseline	70	136	76	134
End Infusion	69	101	76	101
1 hour	66	104	73	106
2 hours	56	107	68	106
4 hours	48	106	64	107
6 hours	39	108	57	106
8 hours	39	104	52	103
End	70	97	76	97

The most commonly used antihypertensives were arteriolar smooth muscle relaxants, calcium channel blockers, ACE inhibitors, central and peripheral acting antiadrenergics, beta blockers and diuretics.

SAFETY

All patients (N = 183) who received at least one dose of drug were evaluated for safety; 90 F and 93 SN.

There were no deaths reported during the study.

Withdrawal for AEs

Ten (11%) F and 12 (13%) SN were withdrawn due to AEs.

The F related events were:

1 Protocol specified hypotension (DBP < 95 mm Hg)
2 Flushing, urinary retention, upset stomach, anxiety, bigeminy, shortness of breath, projectile vomiting
3 Hypokalemia, leg cramps, anxiety, hypotension
4 Tachycardia, headache, nausea/vomiting, insomnia, increased creatinine, increased BUN, hypotension
5 Decreased DBP due to Procardia; maintenance dose was completed
6 Gastrointestinal bleeding and hypotension
7 Hypotension, vomiting, visual disturbances
8 Flushing, headache, nausea and vomiting
9 Agitation and DBP < 95 mm Hg
10 Drop in blood pressure, nausea and parasthesia both arms

SN Events were:

1 Acute hypotension and diaphoresis
2 Hypotension, dizziness and abnormal ECG .
3 Hypotension
4 Hypotension
5 Hypotension
6 Fall in blood pressure, and HR, nausea and restlessness
7 Weakness, feeling faint, paleness and hypotension
8 Paleness, palpitation and sweating
9 Decreased blood pressure, nausea, dizziness, and pain in arm due to blood pressure monitoring cuff
10 Cardiocirculatory collapse, headache, backpain and drowsiness
11 Hypotension

On-Therapy Clinical Events

AEs were reported for 55.6% (50/90) F and 52.7% (49/93) SN patients. Events, by body system, are presented in the Table (from sponsor Table 19 and Appendix 8.1).

Number (%) Patients with Clinical Events, On-Therapy

Body System	F Patients		Events	SN Patients		Events
Cardiovascular	20	22%	22	21	23%	29
General Body	18	20%	21	20	22%	23
Digestive	13	14%	16	14	15%	14
Nervous system	9	10%	9	8	9%	8
Metabolic	8	9%	9	4	4%	4
Psychological	5	6%	6	4	4%	4
Respiratory	5	6%	6	4	4%	4
Integumentary	3	3%	3	6	7%	6
Musculoskeletal	3	3%	3	1	1%	1
Genitourinary	2	2%	2	0	0%	0
Hematic	2	2%	2	5	5%	5

Table 20:

On-therapy/Fenoldopam
Number and Percentage of Patients with Most Common* Clinical Events During Infusion Grouped by Dose at Onset
(Appendix 8.1, 8.1a)

Clinical Event	Dose § (mcg/kg/min) 0.01-0.09 (n=45)		0.1-.39 (n=90)		0.4-.69 (n=44)		0.7-.99 (n=25)		1.0-1.39 (n=18)		>1.39 (n=14)		Total¶ (n=90)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Headache	1	(2.2)	10	(11.1)	0		1	(4.0)	2	(11.1)	1	(7.1)	15	(16.7)
Nausea	1	(2.2)	3	(3.3)	2	(4.5)	0		1	(5.6)	0		7	(7.8)
Decreased Serum K+	0		3	(3.3)	3	(6.8)	0		1	(5.6)	0		7	(7.8)
Flushing	0		3	(3.3)	2	(4.5)	0		0		0		5	(5.6)
Hypotension, other	0		4	(4.4)	0		1	(4.0)	0		0		5	(5.6)
Nausea and Vomiting	0		0		1	(2.3)	1	(4.0)	1	(5.6)	1	(7.1)	4	(4.4)
Extrasystoles, ventricular	1	(2.2)	0		1	(2.3)	1	(4.0)	0		0		3	(3.3)
Decreased Blood Pressure	0		2	(2.2)	0		1	(4.0)	0		0		3	(3.3)
Vomiting	0		2	(2.2)	1	(2.3)	0		0		0		3	(3.3)
Insomnia	0		2	(2.2)	0		0		0		1	(7.1)	3	(3.3)
Cramp, limb	0		2	(2.2)	0		1	(4.0)	0		0		3	(3.3)
Tachycardia, unspecified	0		0		1	(2.3)	1	(4.0)	0		0		2	(2.2)
Pain, general	0		0		2	(4.5)	0		0		0		2	(2.2)
Dyspepsia	0		1	(1.1)	1	(2.3)	0		0		0		2	(2.2)
Dizziness and Giddiness	0		2	(2.2)	0		0		0		0		2	(2.2)
Agitation	1	(2.2)	1	(1.1)	0		0		0		0		2	(2.2)
Anxiety	0		1	(1.1)	1	(2.3)	0		0		0		2	(2.2)
Upper Resp. Disorder, other	0		0		2	(4.5)	0		0		0		2	(2.2)
Hyperhidrosis	0		1	(1.1)	0		0		0		1	(7.1)	2	(2.2)
Total† (per dose range)	2	(4.4)	32	(35.6)	11	(25.0)	7	(28.0)	5	(27.8)	3	(21.4)	50	(55.6)

* "Most Common" is defined as any clinical event that occurred in ≥ 2% of patients within at least one dosing regimen.
§ No clinical events were reported for 8 patients whose infusions began at <0.01 mcg/Kg/min.
¶ Total (per event) may not equal the row sum because one patient may have > one event.
† Total may not equal the column sum because it represents all clinical events per dose range and/or one patient may have > one event.

Table 21:

On-therapy/Nitroprusside
Number and Percentage of Patients with Most Common* Clinical Events During Infusion Grouped by Dose at Onset
(Appendix 8.1, 8.1a)

Clinical Event	Dose§ (mcg/kg/min) 0.1-.49 (n=59)		0.5-.99 (n=92)		1.0-1.49 (n=67)		1.5-3.49 (n=49)		3.5-5.49 (n=10)		5.5-7.49 (n=5)		>7.49 (n=1)		Total¶ (n=93)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Headache	1	(1.7)	3	(3.3)	2	(3.0)	5	(10.2)	1	(10.0)	1	(20.0)	0		15	(16.1)
Nausea	1	(1.7)	1	(1.1)	3	(4.5)	3	(6.1)	0		0		0		8	(8.6)
Hyperhidrosis	1	(1.7)	2	(2.2)	2	(3.0)	1	(2.0)	0		0		0		6	(6.5)
Decreased Blood Pressure	1	(1.7)	0		1	(1.5)	3	(6.1)	0		0		0		5	(5.4)
Hypotension, other	0		2	(2.2)	2	(3.0)	1	(2.0)	0		0		0		5	(5.4)
Dizziness and Giddiness	1	(1.7)	1	(1.1)	1	(1.5)	2	(4.1)	0		0		0		5	(5.4)
Flushing	0		0		1	(1.5)	3	(6.1)	0		0		0		4	(4.3)
Vomiting	0		1	(1.1)	0		2	(4.1)	0		1	(20.0)	0		4	(4.3)
Palpitations	1	(1.7)	0		2	(3.0)	0		0		0		0		3	(3.2)
Somnolence and Drowsiness	0		0		2	(3.0)	1	(2.0)	0		0		0		3	(3.2)
Decreased Serum K+	0		1	(1.1)	0		0		1	(10.0)	0		1	(100.0)	3	(3.2)
Anemia	0		1	(1.1)	0		1	(2.0)	1	(10.0)	0		0		3	(3.2)
Extrasystoles, ventricular	0		0		2	(3.0)	0		0		0		0		2	(2.2)
Ischemic Heart Disease	0		0		0		1	(2.0)	0		1	(20.0)	0		2	(2.2)
Pallor	1	(1.7)	0		0		1	(2.0)	0		0		0		2	(2.2)
Edema	0		0		0		1	(2.0)	1	(10.0)	0		0		2	(2.2)
Tachycardia	0		0		0		2	(4.1)	0		0		0		2	(2.2)
Pain, abdomino-pelvic	0		0		1	(1.5)	0		0		1	(20.0)	0		2	(2.2)
Nausea and Vomiting	0		0		0		0		0		1	(20.0)	0		2	(2.2)
Agitation	0		0		1	(1.5)	0		0		0		1	(100.0)	2	(2.2)
Leukopenia	0		1	(1.1)	0		1	(2.0)	0		0		0		2	(2.2)
Total† (per dose range)	6	(10.2)	13	(14.1)	15	(22.4)	16	(32.7)	3	(30.0)	3	(60.0)	1	(100.0)	49	(52.7)

* "Most Common" is defined as any clinical event that occurred in ≥ 2% of patients within at least one dosing regimen.
§ No clinical events were reported for 14 patients whose infusions began at <0.1 mcg/Kg/min.
¶ Total (per event) may not equal the row sum because one patient may have > one event.
† Total may not equal the column sum because it represents all clinical events per dose range and/or one patient may have > one event.

A listing of AEs, by dose, is presented in sponsor Tables 20 and 21. The most common events were:

	Fenoldopam	Nitroprusside
Headache	17%	16%
Nausea	8%	9%
Decreased serum potassium	8%	3%
Flushing	6%	4%
Hypotension	6%	5%
Nausea/vomiting	4%	2%
Extrasystoles	3%	2%
Dizziness	2%	5%
Hyperhidrosis	7%	2%

Headache occurred mainly at doses of 0.1 - 0.39 and 1.0 - 1.39, and at a time to onset > 6 hours.

Clinical Events within 48 Hours Post-Therapy

AEs were reported for 31% in both groups. Majority of events (10% F and 13% SN) were classified as general body. Listing of events, shown below, is from sponsor Table 22.

Number (%) Events Within 48 Hours Post-Therapy

Body System	F Patients		Events	SN Patients		Events
General Body	9	10%	10	12	13%	13
Metabolic	7	8%	8	3	3%	6
Digestive	6	7%	6	7	8%	8
Cardiovascular	4	4%	5	6	7%	7
Genitourinary	2	2%	4	2	2%	2
Nervous	2	2%	3	3	3%	3
Psychological	2	2%	2	2	2%	2
Respiratory	2	2%	2	1	1%	1
Integumentary	0	0%	0	1	1%	1
Musculoskeletal	1	1%	1	0	0%	0
Hematic	0	0%	0	1	1%	1

The most common events were headache (8% F, 12% SN), constipation (2% F, 5% SN). All other AEs were < 5%. The greatest percentage AEs with F occurred at a dose range of 0.1 - 3.9.

Clinical Events by Time of Onset

Greatest percentage of patients experienced their AEs at intervals > 1 to 6 hours (sponsor Tables 24 & 25).

Severity of Events

Severity of events are summarized, by treatment and by phase below.

Table 24:

FENOLDOPAM

Number and Percentage of Patients with Most Common* Clinical Events Grouped by Time to Onset (Appendix 8.0)

Clinical Event	Time to Onset: On-Therapy: 1st Hour (n=90) n (%)	On-Therapy: >1 Hr-6 Hrs (n=89) n (%)	On-Therapy: >6 Hrs (n=78) n (%)	Post-Therapy: 1st 24 Hrs (n=90) n (%)	Post-Therapy: >1st Day (n=90) n (%)
Headache	1 (1.1)	6 (6.7)	8 (10.3)	4 (4.4)	0
Nausea	3 (3.3)	3 (3.4)	1 (1.3)	0	0
Decreased Serum K^+	0	5 (5.6)	2 (2.6)	1 (1.1)	0
Flushing	4 (4.4)	1 (1.1)	0	0	0
Hypotension, other	1 (1.1)	2 (2.2)	2 (2.6)	0	1 (1.1)
Nausea and Vomiting	0	4 (4.5)	0	1 (1.1)	0
Extrasystoles, ventricular	0	3 (3.4)	0	0	0
Decreased Blood Pressure	0	3 (3.4)	0	0	0
Vomiting	1 (1.1)	2 (2.2)	0	1 (1.1)	0
Insomnia	0	2 (2.2)	1 (1.3)	2 (2.2)	0
Cramp, limb	0	3 (3.4)	0	1 (1.1)	0
Tachycardia, unspecified	1 (1.1)	1 (1.1)	0	0	0
Pain, general	0	2 (2.2)	0	0	1 (1.1)
Dyspepsia	0	2 (2.2)	0	0	0
Dizziness and Giddiness	1 (1.1)	1 (1.1)	0	0	0
Agitation	0	2 (2.2)	0	0	0
Anxiety	0	1 (1.1)	1 (1.3)	0	1 (1.1)
Upper Resp. Disorder, other	1 (1.1)	1 (1.1)	0	0	1 (1.1)
Hyperhidrosis	0	2 (2.2)	0	0	0
§---Total§--- (per interval)	11 (12.2)	30 (33.7)	18 (23.1)	21 (23.3)	12 (13.3)

* "Most Common" is defined as any clinical event that occurred in > 2% of the patient population.

§ Total may not equal the column sum because it represents all clinical events per drug regimen and/or one patient may have > one event.

TABLE 25:

NITROPRUSSIDE

Number and Percentage of Patients with Most Common* Clinical Events Grouped by Time to Onset (Appendix 8.0)

Clinical Event	Time to Onset: On-Therapy: 1st Hour (n=93) n (%)	On-Therapy: >1 Hr-6 Hrs (n=91) n (%)	On-Therapy: >6 Hrs (n=79) n (%)	Post-Therapy: 1st 24 Hrs (n=93) n (%)	Post-Therapy: >1st Day (n=93) n (%)
Headache	3 (3.2)	7 (7.7)	5 (6.3)	7 (7.5)	3 (3.2)
Nausea	0	6 (6.6)	2 (2.5)	1 (1.1)	0
Hyperhidrosis	2 (2.2)	3 (3.3)	1 (1.3)	1 (1.1)	0
Decreased Blood Pressure	1 (1.1)	3 (3.3)	1 (1.3)	0	0
Hypotension, other	1 (1.1)	3 (3.3)	1 (1.3)	1 (1.1)	0
Dizziness and Giddiness	1 (1.1)	2 (2.2)	2 (2.5)	0	1 (1.1)
Flushing	4 (4.3)	0	0	0	0
Vomiting	0	3 (3.3)	1 (1.3)	0	0
Palpitations	2 (2.2)	1 (1.1)	0	1 (1.1)	0
Somnolence and Drowsiness	2 (2.2)	1 (1.1)	0	0	0
Decreased Serum K^+	0	2 (2.2)	1 (1.3)	0	0
Anemia	0	0	3 (3.8)	0	0
Extrasystoles, ventricular	1 (1.1)	1 (1.1)	0	0	0
Ischemic Heart Disease	0	0	2 (2.5)	1 (1.1)	0
Pallor	1 (1.1)	0	1 (1.3)	0	0
Edema	0	1 (1.1)	1 (1.3)	0	0
Tachycardia	0	1 (1.1)	1 (1.3)	0	0
Pain, abdomino-pelvic	0	0	2 (2.5)	0	0
Nausea and Vomiting	1 (1.1)	1 (1.1)	0	0	0
Agitation	0	2 (2.2)	0	0	0
Leukopenia	0	1 (1.1)	1 (1.3)	0	0
---Total§--- (per interval)	14 (15.1)	29 (31.0)	20 (25.3)	18 (19.4)	11 (11.8)

* "Most Common" is defined as any clinical event that occurred in > 2% of the patient population.

§ Total may not equal the column sum because it represents all clinical events per drug regimen and/or one patient may have > one event.

Number of Patients by Severity of AE

	Fenoldopam		Nitroprusside	
	Mild/Moderate	Severe	Mild/Moderate	Severe
On-Therapy				
Hypotension	5	0	4	1
Flushing	5	0	4	0
Hypertension	0	1	0	0
Decreased BP	3	0	5	0
Nausea	5	2	8	0
Vomiting	2	1	3	1
Nausea & vomiting	4	0	2	0
Headache	15	0	15	0
Dizziness	2	0	5	0
Hyperhidrosis	2	0	5	1
Hypokalemia	7	0	3	0
POST-Therapy		4		
Hypotension	1	0	1	0
Hypertension	0	1	0	0
Vomiting	1	0	0	0
Constipation	2	0	5	0
Nausea/vomiting	1	0	0	0
Vomiting	1	0	0	0
Nausea	0	0	1	0
Headache	7	0	10	1
Dizziness	0	0	1	0

Drug Relationship

Number Patients With AEs - Drug Relationship

	Fenoldopam		Nitroprusside	
	Not Related	Related	Not Related	Related
On-Therapy				
Cardiovascular	2	10	2	8
Digestive	1	11	4	4
General Body	9	8	7	11
Genitourinary	1	0	0	0
Hematic	1	1	0	5
Integumentary	0	3	0	1
Metabolic	5	3	1	3
Musculoskeletal	1	2	1	0
Nervous	3	3	1	4
Psychological	2	3	2	1
Respiratory	1	4	1	0

Vital Signs

.e F and 3 SN had SBP < 100 mm Hg on-therapy, and 4 F and 3 SN post-therapy. One F and 4 SN had DBP < 60 mm Hg on-therapy and 5 each group post-therapy. HRs < 60 BPM were seen in 3 F and 15 SN on-therapy and 10 F and 24 SN post-therapy. HRs > 120 bpm were reported in 14 F and 12 SN on-therapy and 4 F and 2 SN post-therapy.

Note: No analysis is given of AEs by sex or age.

Clinical Laboratory Tests

There were 24 patients in each group with lab values above or below sponsor specified levels of concern. There does not appear to be any consistent pattern in these parameters (Sponsor Tables 30 and 31).

In F group, the greatest incidence of low hemoglobin concentrations occurred greater than or equal to one day post-therapy compared to SN which occurred on therapy. Four F patients had values < 80% of lower limit of normal compared to 5 SN. One F had WBC count of concern (> 20 x 10^9/L) two days post-therapy (initial value above normal range: 14.9 rising to 20.1).

Additional changes from baseline included one F with post-therapy hemoglobin 25% below baseline; 36 on- and post-therapy total neutrophil counts 20% below pretreatment values; 8 with platelets 20% below baseline and 39 with WBCs either 25% below or above baseline values.

.N had greater incidence of BUN values of concern compared to F. One F had BUN of concern (> 35 mg/dl) post-therapy (value increased from 30 to 47 mg/dl). Two F had creatinine of concern (2.2 to 4.8, and 2.5 to 3.3); One SGPT increased from 63 to 86 U/L and one alkaline phos from 265 to 298 mU/ml. Three F had glucose values increasing more than 50% (Table 30). There were 18 F with BUN on- or post-therapy values > 50% baseline values. Four had urea > 50% baseline and 4 SGPT 50-100% of baseline. One alkaline phos increased 100% and 2 SGOT were 50-100% of baseline.

F had greater incidence of low serum potassiums than did SN. Five had decreasing serum potassium and 4 with values > 5.5 mmol/L. Four had sodium values of concern.

The percentage of F patients with values below normal at 1 or 2 days post therapy were:

	1 Day Post	2 Day Post
Hemoglobin	10%	13%
Hematocrit	2%	10%
RBC	9%	9%
WBC	- 1%	0%
Neutrophils	4%	5%
Lymphocytes (L)	6%	- 7%
Lymphocytes (H)	5%	7%
Platelets	1%	1%

Table 30:

FENOLDOPAM
Clinical Laboratory Test
of Sponsor-Defined Concern*
(Appendixes 9.2, 11.3)

Laboratory Test	Patient Criteria of Concern	Document Number	Pre-therapy Value	Highest or Lowest Value§	
Hemoglobin (g/dL)	<80% lower limit of normal	6	11.8	8.6	(3dP)
		63	15.9	11.2	(1dP)
		141	12.9	8.7	(4dP)
		164	12.3	9.3	(1dP)
Total neutrophils (nL)	<1.5 nL	98	1.7	1.1	(1dP)
WBC count (10^9/L)	>20 10^9/L	716	14.9	20.1	(2dP)
BUN (mg/dL)	>35 mg/dL	79	30.0	47.0	(1dP)
Creatinine (mg/dL)	2x upper limit of normal	70	2.2	4.8	(2dP)
		160	2.5	3.3	(1dp)
Urea (mg/dL)	>50 mg/dL	539	41.3	59.4	(1dP)
	>0.5 g/L	665	0.4	0.6	(1dP)
ALAT/SGPT (U/L)	>2x upper limit of normal	716	63.0	86.0	(2dP)
Alk. phosphatase (U/L)	>2x upper limit of normal	466	265.0	298.0	(6hP)
Fasting glucose (mg/dL)	>140 mg/dL	17	106.0	183.0	(On)
		100	85.0	156.0	(On)
		137	137.0	152.0	(3hP)
Potassium (mmol/L)	<3.0 mmol/L	53	3.0	2.9	(On)
		59	3.2	2.8	(On)
		112	3.0	2.8	(On)
		141	3.0	2.8	(On)
		162	3.0	2.9	(On)
	>5.5 mmol/L	64	4.4	5.6	(On)
		531	3.7	5.8	(On)
		534	4.0	8.4	(16hP)
		537	5.0	6.5	(3hP)
Sodium (mmol/L)	<130 mmol/L	136	139.0	128.0	(21hP)
		141	131.0	129.0	(On)
		164	143.0	128.0	(1dP)
		539	139.0	128.0	(On)

* Includes values of patients whose pre-therapy results were within the normal range and patients whose pre-therapy values were above or below the normal range but not of sponsor-defined concern.

§ (On) = on-therapy value; (dP) = post-therapy value and number of days post-therapy; (hP) = post-therapy and number of hours post-therapy.

Table 31:

NITROPRUSSIDE
Clinical Laboratory Test Results
of Sponsor-Defined Concern*
(Appendixes 9.3, 11.3)

Laboratory Test	Patient Criteria of Concern	Document Number	Pre-therapy Value	Highest or Lowest Value§
Hemoglobin (g/dL)	<80% lower limit of normal	32	10.1	9.6 (On)
		97	11.7	10.9 (On)
		131	11.6	8.5 (On)
		138	11.6	10.8 (On)
		140	12.4	10.8 (On)
Total neutrophils (nL)	<1.5 nL	163	9.9	8.9 (1dP)
		165	2.5	0.1 (On)
BUN (mg/dL)	>35 mg/dL	463	2.0	1.2 (3hP)
		18	35.0	44.0 (1dP)
		27	30.0	36.0 (1dP)
		60	27.0	45.0 (3dP)
Urea (mg/dL)	>50 mg/dL	158	11.0	93.0 (12dP)
		533	40.0	55.5 (1dP)
		538	30.8	76.2 (1dP)
	>8.3 mmol/L	592	8.1	8.7 (On)
ALAT/SGPT (U/L)	>2x upper limit of normal	143	70.0	73.0 (1dP)
		465	34.0	173 (1dP)
ASAT/SGOT (U/L)	>2x upper limit of normal	60	10.0	96.0 (1hP)
		465	30.0	182.0 (1dP)
Fasting glucose (mg/dL)	>140 mg/dL	39	109	179 (1hP)
(mmol/L)	>7.8 mmol/L	591	ND+	8.1 (On)
Potassium (mmol/L)	<3.0 mmol/L	165	3.0	2.8 (On)
	>5.5 mmol/L	500	4.5	8.7 (1dP)
		532	3.3	7.5 (1dP)
		538	4.0	7.4 (On)
		540	3.9	5.5 (On)
Sodium (mmol/L)	<130 mmol/L	29	133.0	129.0 (22hP)
		717	142.0	128.0 (On)

* Includes values of patients whose pre-therapy results were within the normal range and patients whose pre-therapy values were above or below the normal range but not of sponsor-defined concern.
§(On) = on-therapy value; (dP) = post-therapy value and number of days post-therapy; (hP) = post-therapy and number of hours post-therapy.
+ ND = not done. Patient 591 did not have a baseline fasting glucose drawn.

Percentage of patients with transitions from normal baselines to abnormal values later was:

Percent Patients with Transitions from Normal Baseline Values

Parameter	On-Therapy	0-24 Hr Post	24-48 hr Post
Hemoglobin (L)	10%	15%	19%
Hematocrit (L)	11%	10%	19%
RBC (L)	9%	17%	16%
WBC (L)	0%	3%	2%
Neutrophils (L)	1%	8%	9%
Lymphoctes (L)	22%	15%	6%
Lymphocytes (H)	5%	6%	11%
Platelets	0%	1%	1%

Percentage of F patients with chemistry values outside normal at 1 and 2 days compared to percent at baseline was:

	-1 Day	2 Days
BUN (H)	8%	8%
Alk Phos (H)	- 8%	8%
Creatinine (H)	3%	6%
SGOT (H)	- 1%	- 7%
SGPT (H)	0%	- 5%
Glucose (L)	- 10%	- 4%
Glucose (H)	1%	4%
Bilirubin	5%	- 3%

Percentage of patients with transitions from normal baseline chemistries to abnormal values later was:

Percent Patients with Transitions from Normal Baseline Values

Parameter	On-Therapy	0-24 Hr Post	24-48 hr Post
BUN (H)	5%	18%	18%
Creatinine (H)	4%	6%	13%
Alk Phos (H)	2%	0%	0%
SGOT (H)	5%	8%	3%
SGPT (H)	2%	0%	0%
Glucose (L)	0%	0%	6%
Glucose (H)	20%	10%	19%
Bilirubin (H)	6%	7%	5%

Percentage of F patients with electrolyte values outside normal at 1 and 2 days compared to percent at baseline was:

	-1 Day	2 Days
Potassium (L)	- 4%	- 6%
Potassium (H)	4%	- 2%
Sodium (L)	6%	7%
Sodium (H)	- 1%	2%
Chloride (H)	- 5%	- 5%

Percentage of patients with transitions from normal baseline electrolytes to abnormal values later was:

Percent Patients with Transitions from Normal Baseline Values

Parameter	On-Therapy	0-24 Hr Post	24-48 hr Post
Potassium (L)	22%	9%	10%
Potassium (H)	3%	7%	0%
Sodium (L)	28%	17%	15%
Sodium (H)	0%	0%	1%
Chloride (H)	3%	3%	3%

Safety - ECGs

The following ECG parameters were evaluated: atrial rate, ventricular rate, PR, QRS and QTc intervals. Mean values are presented in the Table (sponsor Table 44). There were sporadic changes in T wave morphology and ST segments and rate changes. Sponsor states that this may be due to improvements in hypertension. There were two cases of ventricular premature beats with F.

ECG Average Change from Baseline

Parameter	Baseline	6 hrs on	24 hrs post	48 hrs post
Fenoldopam				
Atrial rate	87.5	0.8	- 6.8	- 9.7
Ventric rate	87.4	0.8	- 6.7	- 9.5
PR interval	160.1	0.1	2.5	1.8
QRS interval	122.1	- 1.8	- 12.2	1.0
QTc interval	437.1	9.5	- 3.0	- 11.7
Nitroprusside				
Atrial rate	82.2	0.3	- 7.3	- 6.5
Ventric rate	82.9	0.2	- 7.3	- 6.5
PR interval	165.4	- 3.3	3.7	- 3.3
QRS interval	131.9	1.2	- 20.4	- 10.3
QTc interval	439.4	9.6	6.0	- 4.1

At baseline, 27/84 (32%) had T wave abnormalities (flattening, inversion or peaking). During F infusion, majority remained unchange (96%). Eight patients experienced new T wave abnormalities or worsening of the previous condition. Resolution of baseline abnormalities did not occur during infusion. During post-therapy, 9% at 24 hours and 24% at 48 hours had improvements from baseline.

ST segment changes were present in 34/84 (40%) at baseline. Majority showed no change both during infusion and post-infusion.

Rebound Hypertension

There were 3% in both groups with DBP exceeding baseline during down-titration or post-treatment. All the patients were receiving antihypertensives concomitantly during this period.

Sponsor Conclusions

Sponsor states " .....F and not SN infusions were effective in producing dose-related decreases in elevated DBP which were sustained during a maintenance infusion....". It then states "These clinically important changes in DBP from baseline elicited by F were not statistically significant different from similar reductions elicited with infusions of SN, demonstating that F to be as efficacious as SN in lowering elevated blood pressure..". (These two statements are, obviously, not compatible).

Reviewer's Comments

1 This report is not reader friendly, especially regarding the numbering and order of Tables and appendices, which are not always in the same order as cited in the report. Some Tables were not even referenced in the text.
2 This is an open label comparison, with investigators deciding on the effectiveness of the drugs. Being open label, there is a possibility of bias, especially as the patient did not have to necessarily reach a specific decrease in DBP to be regarded as a success. The investigator could claim a succes if he thought that the decrease was sufficient without reaching the protocol specified target.
3 The use of concomitant antihypertensive medications during maintenance, down titration and post-therapy, while obviously ethical does confound the interpretation of data at these time intervals.
4 Patients withdrawn for lack of efficacy should be analyzed together with "treatment failures".
5 Sponsor's conclusion that F, and not SN, was effective is incorrect. Both drugs were similar in reducing DBP.
6 Lab data are difficult to interpret in view of the short duration of the trial
7 No safety data are supplied by age or sex.
8 Decrease in DBP was more pronounced in patients receiving concomitant hypertensives than in the group not receiving additional therapy.
9 A subgroup analysis should be done on patients who receiving previous antihypertensives versus those who did not and the timing of previous therapy.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NOV 1990

NDA Number: 19-922
Drug Name: Fenoldopam
Sponsor:

Submission Date: October 17, 1990
Submission Type: Safety Update
Date of Receipt: October 24, 1990
Review Complete: November 9, 1990

Content: Safety Update

Background: The NDA was completed and previously reviewed. This is a safety update with a cutoff date of June 13, 1990 for the iv formulation.

Review: The submission was reviewed. There does not appear to be any additional safety problems that were not seen in the original submission, except for reports of increased intraocular pressure seen in a number of patients. This was previously submitted and reviewed. FDA consultant has issued an opinion on these cases.

Recommendations: 1 This submission is a safety update with no new serious events having been identified, except for cases of increased intraocular pressure. There is nothing new in the review to alter previously expressed opinions regarding this NDA.

Signature:

BFriedman
9 Nov 90

cc:
Original NDA
HFD-110/Division File
HFD-110/CSO
HFD-110/C Graham

FENOLDOPAM - SAFETY UPDATE

The sponsor has submitted 59 volumes in this safety update, with a cutoff date of June 13, 1990 for the iv formulation

Since the submission of the NDA, two additional hypertension studies were completed with 112 fenoldopam and 93 nitroprusside patients. The data are presented separately for these studies as well as combined for all studies, including non-hypertension indications and oral dosing.

OVERVIEW

Overall Extent of Exposure

As of June 13, 1990, 802 patients and subjects had received fenoldopam [illegible]; 70 patients and 15 subjects received both iv administration. Overall a total of 1040 were exposed to fenoldopam. The exposure data are summarized in the Table, as extracted from sponsor's Table 1.1.

Exposure to Fenoldopam

Route of Administration	Patients	Subjects	Total
Intravenous	598	204	802
Severe hypertension	320		
Mild/moderate hypertension	64		
Other diagnoses	214		
TOTAL			

* 70 patients and 15 subjects received both forms of administration and are counted under both routes but only once in the total.

Intravenous Studies

In the two additional studies (@) since submission of the NDA, 112 patients received fenoldopam for a mean duration of infusion of 9 hours 19 minutes; majority received drug from 1 to 12 hours. About 75% had maximum infusion rates within 0.1 to 0.69 mcg/kg/min range. (Unit mcg/kg/min will be omitted in the remainder of this report). About 34% of patients received the maximum infusion rate from 30 minutes to 4 hours and 47% (53/112) for longer than 4 hours. Majority (84/112, 75%) had cumulative doses of 2.5 to 30 mg.

(@) additional studies called "interval data"

In the combined data, exposure for 320 patients in 9 severe hypertension studies were evaluated. Mean duration was 7 hours 56 minutes; overall exposure 1 to 24 hours, with majority being between 1 and 12 hours. Maximum infusion rates were 0.1 to 0.69 with 55% receiving maximum dose for 4 hours and 28% (90/320) exceeding 4 hours at maximum dose; cumulative dose was 2.5 to 30 mg for 72% of patients.

In the controlled hypertension studies, nitroprusside, nitroglycerin or placebo, the mean duration of exposure with fenoldopam and nitroprusside was the same: 7 hours 3 minutes vs 7 hours 37 minutes, respectively; nitroglycerin exposure was 1 hour 17 minutes and placebo 3 hours 1 minute.

In non-hypertension studies, 214 patients with CHF, renal or hepatic disease received iv drug; 149 were in open, non-crossover studies with mean exposure of 15 hours 52 minutes. The other 65 received drug in randomized, crossover studies with mean duration of 4 hours 15 minutes.

There were 204 subjects who received iv fenoldopam in crossover (79) and non-crossover (125) studies. Mean duration in non-crossover studies was 2 hours 58 minutes and for crossover it was 7 hours 53 minutes. Majority (95%) had duration of exposure of 1 to 12 hours. (Comment: This is a wide range, 12 hours). Orally, fenoldopam had been administered to 2225 patients and subjects. Daily doses of 25 to 600 mg were given to 1930 patients, with exposure from one to 1147 days with 434 patients being treated for > 180 days. There were 293 subjects with dosing from one to 30 days.

Demography

Mean age for patients was 55.6 years (17 to 88) and for subjects 28.3 (18 to 56). Males comprised 65% of the population and caucasians 65%, blacks 12% and other races 12%.

Adverse Experiences

Incidence of AEs with iv fenoldopam was less than with oral form (44% vs 62% patients; 45% vs 61% subjects). Most commonly affected body system was cardiovascular.

With iv infusion in short term studies, 263/598 (44%) patients and 91/204 (45%) subjects reported AEs. The events in severe hypertension were considered to be mild to moderate severity (89%) and drug related (78%). Cardiovascular events were reported in 24% of severe hypertensives, 19% moderate hypertensives, 18% other studies and 28% subjects. Most common events was flushing (10% of severe hypertensives). Flushing was reported in 5% of mild to moderates and 2% in other studies; incidence in subjects was 25%. In mild to moderate hypertensives, abnormal ECGs was seen in 13% compared to 4% in severe hypertensives. In the "other" studies, hypotension was the most common event (9%) compared to 4% in severe hypertensives.

General body events were second most common, especially headache (45% severe hypertensives, 9% mild/moderates, 6% "others" and 15% subjects). Other events included decreased potassium (6% severes) and nausea (4%).

Sponsor states that the incidence of AEs was similar to nitroprusside in controlled studies (52% fenoldopam vs 51% nitroprusside).

Number (%) Patients with AEs (Sponsor Table 1.2)

	Update		NDA	
Severe hypertension	155/320	48%	94/208	45%
Mild/moderate	20/64	31%	20/64	31%
Other indications	88/214	41%	52/111	47%
Subjects	91/204	45%	82/170	48%
Fenoldopam totals	354/802	44%	248/553	45%
Nitroprusside totals	57/112	51%	19/39	49%

Post-therapy AEs, occurring within 48 hours after the studies were less frequent than on-therapy events in severe hypertension (33% post vs 48% on-therapy). The only body system with increased events post-therapy was hemic. Most common post-therapy AEs were headache, insomnia and increased BUN and creatinine.

After oral administration, 1195/1930 (62%) patients and 178/293 (61%) subjects had on-therapy AEs.

12. AE nominal cause for WD. but U.S. also "concern"

Six of 320 severe hypertensives had blood pressure or heart rate measurements of sponsor-defined concern, resulting in withdrawal from the study. Ten patients (3%) had BP readings of concern with 4 having associated AEs resulting in withdrawal. There were 34 (11%) with HR readings of concern (>120 bpm) and 31 (10%) with HRs < 60 bpm, with one being withdrawn.

HR/BP (6)

Post-therapy, 18/301 severe hypertensives (6%) had BPs of concern with 5 reporting hypotension. There were 11 (4%) severe hypertensives with HRs > 120 bpm, one with associated atrial fibrillation. HRs < 60 bpm were seen in 63 (21%) of severe hypertensives.

Withdrawals Due to AEs

In the new studies, 24 patients were withdrawn due to AEs, 11 received fenoldopam. Most common causes were hypotension, decreased diastolic BP. Of the total 802 patients/subjects, 5% withdrew due to AEs. In oral study update, 86 were withdrawn for AEs in non-hypertension studies, 78 CHF and 8 renal failure. Of these 53 received fenoldopam. In oral studies, placebo patients withdrawn were 12 CHF, 2 renal failures.

To date, of 2223 patients/subjects receiving fenoldopam up to 1174 days, 507 (23%) were withdrawn due to AES.

Deaths

Since submission of 120 day update, one iv CHF patient died of ventricular fibrillation. This was considered possibly drug related. Four died within 30 days post-therapy, all considered unrelated to fenoldopam. There were 21 deaths with oral fenoldopam (19 CHF and 2 renal failure); 18 were considered unrelated to drug and 3 possibly related. One death occurred after 21 days therapy and the rest after 30 days treatment. Eleven oral patients died 30 days post-therapy, all considered unrelated to drug.

For total experience to date, one iv died on therapy, 10 within 30 days post-therapy; 72 oral died on-therapy (61 considered unrelated to fenoldopam); 20 died within 30 days post-therapy.

Clinical Laboratory Results

Sponsor states that there were no safety issues associated with lab data trends for iv fenoldopam. Most common abnormal finding was elevations in renal function tests. (This conclusion will be examined on review of the data). There were decreases in total neutrophil counts and changes in platelet counts.

Dose-Response Information

AEs increased with dose increase, 4% with infusion rates < 0.1 and 19-29% at higher rates. Higher cumulative doses resulted in more AEs. Nausea was more common with higher infusion rates, as were headache and flushing.

Drug-Drug Interactions

AEs were more common when prior thepapy was centrally acting antiadrenergics.

Drug-Demographic Interactions

Blacks experienced higher incidence of post-therapy events than non-blacks. Age did not appear to be a problem but more females reported on-therapy AEs than did males.

Drug-Disease Interactions

No specific drug-disease problems were identified.

AEs Not from Clinical Trials

Literature search has identified publications reporting increased ocular pressure, without symptoms, associated with fenoldopam. Values returned to baseline on discontinuation of the infusion.

Conclusion

Sponsor concludes that fenoldopam is a safe drug for iv infusion.

FENOLDOPAM - SAFETY UPDATE

Overall Extent of Exposure

As of June 13, 1990, 802 patients/subjects had received iv fenoldopam
70 patients and 15 subjects received both iv
A total of 598 patients and 204 subjects received iv fenoldopam, of whom 384 were in hypertension studies (320 severe hypertensives). This total is an increase of 187 patients and subjects compared to September 30, 1988 database.

Iv Experience in Severe Hypertension

The sponsor has reported all findings in two groups, "Interval data" and "Combined data". The interval data refer to patients from two studies with 112 severe hypertensives conducted since December 12, 1988; combined data are all studies reported.

Interval Data

This data base consists of 112 severe hypertensives in two studies. Mean duration of infusion for both studies combined was 9 hours 19 minutes with majority being infused for 1 to 12 hours. (As stated previously, this a wide range). Majority (75%) had infusion rates within 0.1 to 0.69 mcg/kg/min and 91/112 (81%) maintained their maximum rate for > 30 minutes. Thirty-eight (34%) received maximum rate for 30 minutes to 4 hours and 47% for > 4 hours. Cumulative doses of 2.5 to 30 mg were seen in 84/112 (75%) with 18 (16%) exceeding 30 mg. Expressing cumulative dose as mg/kg, 92% (103/112) had cumulative doses of 0.001 to 0.500 mg/kg.

Combined Data

A total of 320 severe hypertensives were evaluated. Mean duration of infusion was 7 hours 10 minutes (range of majority 1-12 hours). Maximum infusion rate was 0.1 to 0.69 for 76% (244/320) and 83% maintained their maximum ratte for > 30 minutes. Majority, 55%, received maximum dose up to 4 hours with 28% exceeding 4 hours. About 72% had cumulative doses of 2.5 to 30 mg with 93% being 0.001 to 0.500 mg/kg.

Controlled Studies

One controlled study in "INTERVAL DATA" compared fenoldopam to nitroprusside. Mean duration of exposure for 90 fenoldopam patients was 9 hours 28 minutes compared to 9 hours 19 minutes for 93 nitroprusside group. About 83-85% in both groups were exposed for 6-24 hours.

In 5 controlled studies in "Combined Data", fenoldopam was compared to nitroprusside, nitroglycerin or placebo. Mean durations were: fenoldopam 7 hours 3 mintes, nitroprusside 7 hours 37 minutes, nitroglycerin 1 hour 17 minutes and placebo 3 hours 1 minute.

In Non-Hypertension studies, 214 CHF, renal or hepatic disease patients received iv fenoldopam in crossover and non-crossover studies. In non-crossover, 149 patients had mean duration of 15 hours 52 minutes compared to 65 in randomized crossover studies with duration of infusion of 4 hours 15 minutes. (Why was duration in open label, non-crossover studies almost 4 times as long than crossover ?).

There were 204 subjects given iv fenoldopam, 125 in non-crossover trials. Mean duration of infusion was 2 hours 58 minutes (non-crosover) and 7 hours 53 minutes (crossover).

Total Exposure IV Fenoldopam

Fenoldopam was administered iv to 802 patients and subjects with duration of exposure shown in the Table (sponsor's Table 2.1).

Mean and Median Duration of Exposure IV Fenoldopam

		Duration exposure (hours:minutes)		
Diagnosis	Patient/Subject	Mean	Median	Range
Hypertension (384)				
Non-crossover	353	08:08	06:01	
Crossover	31	02:08	01:56	
Non Hypertension (214)				
Non-crossover	149	15:52	23.40	
Crossover	65	04:15	04:02	
Subjects (204)				
Non-crossover	125	02:58	2:00	
Crossover	79	07:53	05:55	

Exposure in Severe Hypertension

The interval data consist of 112 patients in two protocols (A52, D1101). In A 52, all 22 patients had total cumulative doses of 1.32 to 34.15 mg with total duration of infusion of ± 8.5 hours (3-17 hours). In D1101, all 90 patients had infusion durations of 1-29 hours (mean 9 hours). Total cumulative doses were 0.45 to 132 mg.

Combined data: There were 8 dose titration studies with [illegible] patients. In A14, all 26 patients had total cumulative doses between 2.0 and 11.0 mg and durations of 2-12 hours. In the other, previously reported studies, the total cumulative doses ranged from 0.25 to 1v4.4 mg with infusion durations of 2 to 44.6 hours. (Each study had its own titration scheme, duration of therapy and maximum rate. These numbers were taken from the report of each study to provide an overall range. The protocols, in general, were specifying a duration of infusion up to 24 hours, but certain patients were treated in excess of protocol specifications).

Total Duration of Exposure

In the two "interval" studies, total duration of exposure ranged from 55 minutes to > 28 hours. In combined data, mean exposure was 7 hours 56 minutes (range 26 minutes to 6 days). Distribution of exposure was: < 2 hours = 19 (6%); 2-6 hours = 136 (42%); > 6-12 hours = 122 (38%); > 12 to 24 hours = 34 (11%); > 24 hours = 9 (3%). In one study, E 67, 5 patients (12%) had durations > 24 hours.

Maximum Infusion Rate

In the "interval data", the mean maximum infusion rates (mcg/kg/min) were 0.44 ± 0.04 in study A52 (range 0.10-0.90), and in D1101 the mean was 0.61 ± 0.06 (range 0.01 to 2.90). The distribution of maximum infusion rates in the combined data has a mean of 0.50 ± 0.02 with a range of 0.05 to 2.90. A total of 76% (244/320) had maximum infusion rates of 0.1 to 0.69. The distribution of maximum infusion rates for combined data was: < 0.1 = 3 (1%); 0.1 - 0.69 = 244 (76%); 0.7 - 1.5 = 59 (19%); > 1.5 = 14 (4%).

Cumulative Dose (mg)

The cumulative doses in the two "interval" studies had a mean of 13.99 (range 1.32-34.15 mg) in A52 and 19.1 (0.45-132 mg) in D1101. In both studies, 75% received cumulative doses between 2.5 - 30 mg; two patients in D1101 had doses > 100 mg.

Mean cumulative dose in combined data base was 14.4 ± 1.2, range 0.25-185.8 mg. The distribution of dose was: < 2.5 = 55 (17%); 2.5-10.0 = 140 (44%); > 10-30 = 88 (28%); > 30-50 = 20 (6%); > 50 mg = 17 (5%).

Time (minutes) to Maximum Infusion Rate

No data are supplied in this section as sponsor felt it did not present important new data.

Time (minutes) on Maximum Infusion Rate

Distribution of time on maximum infusion for the two interval studies ranged from 30 minutes to > 4 hours in A52 and 10 minutes to > 4 hours in D1101. Most (81%) in both studies were on for > 30 minutes. In D1101, 42% exceeded 4 hours. The distribution of time on maximum dose for the combined data was: < 11 minutes = 17 (5%); 11-30 minutes = 36 (11%); 31-60 = 80 (25%); 121-240 = 51 (16%); > 240 minutes = 90 (28%).

61-120 ?

Cumulative Dose (mg/kg) & Total Duration of Infusion

In interval data, 73% received total cumulative dose between 0.0011 and 0.25 mg/kg. Of these, 96% had total duration of infusion of 1-12 hours. Nine had doses > 0.5 mg/kg with 7 having duration of 12-24 hours.

For combined data, 80% (257/320) received total cumulative dose between 0.0011 and 2.5 mg/kg. Of these, 95% (245/257) had total duration 1-12 hours. Twenty-three had total dose > 0.5 mg/kg. Distribution of doses were: 0.0011 to 0.0500 = 96 (30%); 0.0501 to 0.1000 = 77 (24%); 0.1001 to 0.2500 = 84 (26%); 0.2501 to 0.5000 = 40 (13%); > 0.5000 = 23 (7%).

Comparison Medication Exposure in IV Controlled Trials

Interval data had one open, controlled trial with 90 patients receiving fenoldopam and 91 nitroprusside. Mean duration fenoldopam was 9 hours 11 minutes (range 38 minutes to 28 hours 16 minutes) and for nitroprusside it was 9 hours 19 minutes (range 23 min - 30 hours 44 minutes).

In combined database, a total of 148 patients received fenoldopam with mean duration of 8 hours 11 minutes; 132 nitroprusside patients had mean duration of 10 hours 8 minutes and 5 nitroglycerin patients mean exposure was 1 hour 17 minutes. (The 10 placebo patients exposure was 3 hours) ?

(6) appendix 2.7.17 gives fenoldopam = 7.63 and prussde = 7.37

Total Duration of Exposure for All subjects Receiving IV Fenoldopam

This appears in Table on page 6. Total 204 subjects received drug; duration was 1-12 hours for 95% subjects.

Demograph.

A total of 2458 patients and 482 subjects received fenoldopam by 11 June 1990. The mean age was 55.6 years (17 to 88 years) for patients and 28.3 (18 to 56) for subjects. There were 1591 (65%) male patients and 80% male subjects. Caucasians were 65%, blacks 23% and 12% other races. Race was not reported for subjects.

There were 112 severe hypertensives in the "interval phase" with a mean age of 48.3 years; 51% males, 49% caucasians and 51% black..

Of the 2458 patients and 482 subjects receiving fenoldopam, 717 (24%) received only iv administration, 2137 (73%) only and 86 (3%) both iv and

Distribution of Patients by Route of Administration, Age and Race

Route	N	Mean Age	Range	Caucasian	Black	Other
IV only	628	49.4	17-80	291 (59%)	231 (44%)	16 (2%)
IV +	70	63.8	29-88	65 (93%)	5 (7%)	0 (0%)
TOTAL	2458	55.6	17-88	1597 (65%)	558 (23%)	303 (12%)

Severe Hypertension

These data are from 320 severe hypertensives. the mean age was 49.4 years (17-80), with 56% males, 48% caucasians and 50% black; mean baseline weight was 80.5 kg (45-179).

Adverse Experiences

Incidence of clinical events for patients and subjects was 44% and 45%, respectively with iv form and 62% and 61% respectively for oral.

IV Fenoldopam

Of the 263 (44%) patients with AEs, 155/320 (48%) were severe hypertensives and 20/64 (31%) mild to moderates and 88/214 (41%) other (CHF, renal or hepatic diseases). Majority of events were considered mild to moderate and drug related in 78% of cases.

Most common therapeutic area was cardiovascular (24% of severe hypertensives, 19% mild/moderate and 18% other). Flushing was the most commonly reported event for severe hypertensives. In mild/moderate, abnormal ECGs was most common. Second most common system was general body with headache being the main event.

Compared to nitroprusside, the incidence of AEs was similar (52% vs 51%).

ADVERSE EXPERIENCES

In severe hypertension studies using interval data, 123 AEs were reported in 61/112 patients receiving iv. In combined data, a total of 285 AEs were reported for 155/320 (48%) patients. These data are presented below (Sponsor's Table 4.1).

Number (%) Fenoldopam Patients with On-Therapy Clinical Events in Severe Hypertension Studies (Nell30).

Body System	Number of Patients		Number of Events
Cardiovascular	76	24%	96
Digestive	28	9%	35
General Body	56	18%	60
Genitourinary	9	3%	10
Hematic	3	1%	3
Integumentary	6	2%	6
Metabolic	21	7%	25
Musculoskeletal	8	3%	8
Nervous	23	7%	23
Psychological	8	3%	9
Respiratory	10	3%	10
TOTAL	155	48%	285

Clinical Events by Incidence

The most frequently reported AEs in the interval studies were headache (20%), flushing (9%), decreased serum potassium (8%), nausea (6%), hypotension (5%), and ventricular extrasystoles (4%). One patient was withdrawn from the study due to headache.

In the combined data base of 320 severe hypertensives with iv fenoldopam, headache was the most commonly reported event (14%), followed by flushing (10%), decreased serum potassium (5%), hypotension (4%), ventricular extrasystoles (4%) and nausea (4%). These data are presented in sponsor's Table 4.3. Sponsor feels that flushing, headache and hypotension are predictable secondary effects of the vasodilatory action of fenoldopam.

Table 4.3: Rank-order of On-therapy Clinical Events* for Fenoldopam Patients in Severe Hypertension Studies (Appendix 4.1, 4.2)

Clinical Event	*Interval Data:* Number of Patients	%	*Combined Data:* Number of Patients	%
Headache	22	(20)	45	(14)
Flushing	10	(9)	33	(10)
Decreased serum potassium	9	(8)	18	(6)
Hypotension+	5	(5)	14	(4)
Ventricular extrasystoles	4	(4)	14	(4)
Nausea	7	(6)	14	(4)
Dizzyness	3	(3)	11	(3)
Vomiting	3	(3)	9	(3)
Tachycardia	4	(4)	8	(3)
Limb cramp	3	(3)	8	(3)
Upper respiratory disorder	2	(2)	7	(2)
Blood pressure decreased+	3	(3)	7	(2)
Abnormal ECG	0	(0)	7	(2)
Palpitations	1	(1)	5	(2)
Nausea and vomiting	5	(5)	5	(2)
Hyperhidrosis	3	(3)	5	(2)
Anxiety	2	(2)	4	(1)
Dyspepsia	2	(2)	3	(1)
Abdomino-pelvic pain	0	(0)	3	(1)
Precordial pain	0	(0)	3	(1)
Insomnia	3	(3)	3	(1)
Total Number of Clinical Events	123		285	
Total Number of Patients with Clinical Events	61	(54)	155	(48)
Total Number of Patients Receiving Fenoldopam	112	(100)	320	(100)

* Includes events reported for at least 1% of patients in COMBINED DATA set. Rank ordered based on COMBINED DATA set.

\+ The dictionary preferred term "hypotension" includes only reductions in blood pressure specifically designated as hypotensive by the investigator; see also "blood pressure decreased."

Investigator-Determined Relationship to Pentoxapam

Of 133 interval AEs for 61 patients, 73% were considered drug related or possibly related. Of 285 AEs in the combined database (155 patients), 78% were considered either related or possibly related. The data in the following Table are summarized from sponsor's Table 4.4.

Number On-Therapy AEs in Severe Hypertensives - Investigator Determined

Body System	Not Related		Possibly Related		Related	
Cardiovascular	6	2%	11	9%	51	18%
Digestive	7	2%	22	8%	6	2%
General Body	19	7%	24	8%	16	6%
Genitourinary	6	2%	3	1%	1	<1%
Hematic	1	<1%	1	<1	1	<1%
Integumentary	0	0%	3	1%	3	1%
Metabolic	9	3%	16	6%	0	0%
Musculoskeletal	1	<1%	7	2%	0	0%
Nervous	5	2%	7	2%	9	3%
Psychological	4	1%	5	2%	0	0%
Respiratory	1	<1%	8	3%	1	<1%
TOTAL AEs	59	21%	134	47%	88	31%

Investigator Determined Severity

Majority (89%) AEs in the interval studies were considered mild (55%) or moderate (33%). Ten AEs in 7 patients were considered severe. Three patients were withdrawn: flushing and tachycardia 3 hours after start of infusion; vomiting after 4 hours 35 minutes; nausea after 50 minutes. In the combined data, 89% were considered mild or moderate in severity. Twenty six AEs (15 patients) were considered severe with 6 patients being withdrawn from the studies. Classification by severity is presented below, summarized from sponsor's Table 4.5.

Number of AEs by Investigator Determined Severity

Number On-Therapy AEs in Severe Hypertensives - Investigator Determined

Body System	Mild		Moderate		Severe	
Cardiovascular	57	20%	11	9%	51	18%
Digestive	7	2%	22	8%	6	2%
General Body	19	7%	24	8%	16	6%
Genitourinary	6	2%	3	1%	1	<1%
Hematic	1	<1%	1	<1	1	<1%
Integumentary	0	0%	3	1%	3	1%
Metabolic	9	3%	16	6%	0	0%
Musculoskeletal	1	<1%	7	2%	0	0%
Nervous	5	2%	7	2%	9	3%
Psychological	4	1%	5	2%	0	0%
Respiratory	1	<1%	8	3%	1	<1%
TOTAL AEs	59	21%	134	47%	88	31%

A listing of the 17 severe AEs is presented in sponsor's Table 4.6

Table 4.6: Individual Patients in Severe Hypertension Studies with On-therapy Clinical Events Designated Severe by the Investigator

Study Number	Patient Document Number	Clinical Event	Outcome
INTERVAL DATA:			
A52	101	Flushing Tachycardia	Withdrawn for clinical event
	302	Nausea & vomiting Hyperhidrosis Headache	Completed
	303	Flushing	Completed
D1101	6	Hypertension	Withdrawn for insufficient therapeutic effect
	56	Vomiting	Withdrawn for clinical event
	79	Nausea	Completed
	502	Nausea	Withdrawn for clinical event
NDA DATA:			
A14	104	Dizziness Migraine Headache	Withdrawn for clinical event
B63	63	Decreased blood pressure Flushing Hyperhidrosis	Completed
B63	45	Leg cramps	Completed
B63	173	Anxiety	Completed
B67	2111	Facial cyanosis Head and neck symptoms	Completed
B69	4052	Decreased blood pressure Presyncope Dizziness	Withdrawn for clinical event
B85	46	Hypotension[§] Hyperhidrosis	Withdrawn for clinical event
B85	15	Hypertension	Withdrawn for insufficient therapeutic effect

§ The dictionary preferred term "Hypotension" includes only reductions in blood pressure specifically designated as hypotensive by the investigator.

Time to Onset of AEs

Sponsor maintains that time of onset is of little value in short term studies, but presents data in any event. About 67% of AEs in interval data occurred within first 6 hours of infusion; 16% had at least one event reported during the first hour with majority 38% within the 1-3 hour period. Flushing was reported most frequently within the first 3 hours, as was dizziness.

In the combined data, 66% were reported during the first 6 hours, of whom 26% were within first hour and majority (45%) in 1-3 hour period. A review of sponsor's Table 4.7 shows that 9% of cardiovascular events occurred within 0-1 hours and 10% within 1-3 hours. Digestive (4%) and general body (7%) were mainly during 1-3 hour interval and metabolic (5%) occurred at 6-12 hours.

Ventricular extrasystoles, flushing and tachycardia were mainly reported during first three hours of infusion. Hypotension and decreased blood pressure were throughout the study but mainly within 1-3 hour period. Headache occurred mainly after 1 hour, metabolic events after 3 hours and dizziness at 0-1 and 1-3 hours.

Post-Therapy Events - Severe Hypertension

In the interval group, 173 AEs were reported pre-, on- and post-therapy for 112 patients. There were 12 pre-, 123 on- and 38 post-therapy events. Distribution of post-therapy AEs by body system were mainly general body and metabolic. The incidence post- was lower than on-therapy (22% vs 54%). Comparison of on- and post-therapy events is summarized from sponsor's Table 4.10.

Number Patients with AEs On- and Post-Therapy

Body System	On-Therapy			Post-Therapy		
	Events	Patients		Events	Patients	
Cardiovascular	96	76	24%	32	28	9%
Digestive	35	28	9%	15	13	4%
General Body	60	56	18%	28	26	8%
Genitourinaryy	10	9	3%	20	12	4%
Hematic	3	3	<1%	18	14	4%
Integumentary	6	6	2%	0	0	0%
Metabolic	25	21	7%	32	21	7%
Musculoskeletal	8	8	3%	2	2	<1%
Nervous	23	23	7%	25	22	7%
Psychological	9	8	3%	4	4	1%
Respiratory	10	10	3%	3	3	1%
Total AEs	285	155	48%	179	106	33%

During the 48 hour post-therapy period, the most commonly reported events were headache (7%), insomnia (4%), increased BUN (3%), dizziness, abnormal WBC, urinary casts, constipation, increased creatinine, decreased potassium, abnormal ECG, hematuria 2% each.

On-Therapy AEs in Controlled Hypertension Studies.

In the one controlled, open label, interval study, 56% fenoldopam patients reported AEs compared to 52% nitroprusside group. The incidencies of flushing, headache, vomiting and nausea were similar in the two groups. Decreased serum potassium was more common with fenoldopam while dizziness and somnolence were more frequent with nitroprusside.

Using combined data for all studies (severe and moderate hypertension), 47% fenoldopam patients reported AEs compared to 51% nitroprusside. Using data from severe hypertension studies only, 56% fenoldopam patients reported AEs compared to 51% nitroprusside. Data are summarized, for all controlled studies, as follows:

Treatment	Number receiving drug	Number with AEs	
Fenoldopam	141	70	47%
Nitroprusside	111	57	51%
Placebo	13	0	0%
Nitroglycerin	5	0	0%

Compared to nitroglycerin alone, the incidence of AEs was 52% vs 51% respectively. Comparison of AEs in these two groups is presented in sponsor's Table 4.13. As may be seen, there is no major differences in the incidence of AEs between the two regimens.

On-Therapy AEs for Patients Receiving IV Fenoldopam in Other Studies

There were 164 AEs reported in 41% patients receiving fenoldopam for other indications (CHF, renal and hepatic diseases). Percentage of patients, by body system, reporting AEs is listed below (sponsor's Table 4.15).

Number Patients with AEs (Other Studies).

Body System	Number Patients (N=214)		Number Events
Cardiovascular	39	18%	46
Digestive	23	11%	27
General Body	32	15%	34
Genitourinary	6	3%	7
Hematic	6	3%	7
Integumentary	1	<1%	1
Metabolic	14	7%	16
Musculoskeletal	1	<1%	1
Nervous	10	5%	10
Psychological	2	1%	2
Respiratory	12	6%	13
TOTAL	88	41%	164

The main events reported were hypotension (9%), nausea (8%), headache (6%), dyspnea (4%), vomiting, flushing, pyrexia, decreased potassium and insomnia 3% each and dizziness 2%.

Table 4.13: Rank-order of Clinical Events in Positive-Controlled Hypertension Studies with Nitroprusside (Studies L42*, B74, and D1101) (Appendixes 4.2, 4.9, 4.9A and 4.10)

	INTERVAL DATA				COMBINED DATA			
	Fenoldopam		Nitroprusside		Fenoldopam		Nitroprusside	
Clinical Event		(%)		(%)		(%)		(%)
Headache	15	(17)	13	(14)	19	(15)	19	(14)
Nausea	7	(8)	8	(9)	11	(8)	10	(8)
Flushing	5	(6)	4	(4)	10	(8)	9	(7)
Decreased serum potassium	7	(8)	3	(3)	8	(6)	5	(4)
Hypotension+	5	(6)	5	(5)	7	(5)	13	(10)
Vomiting	3	(3)	4	(4)	6	(5)	6	(5)
Nausea and vomiting	4	(4)	1	(1)	4	(3)	1	(1)
Dizziness	2	(2)	5	(5)	4	(3)	6	(5)
Limb cramp	3	(3)	0	(0)	4	(3)	0	(0)
Ventricular extrasystoles	3	(3)	2	(2)	4	(3)	2	(2)
Decreased blood pressure	3	(3)	5	(5)	3	(2)	5	(4)
Insomnia	3	(3)	0	(0)	3	(2)	0	(0)
Palpitations	1	(1)	3	(3)	2	(1)	3	(2)
Dyspepsia	2	(2)	0	(0)	2	(1)	0	(0)
Visual disturbance	1	(1)	0	(0)	2	(1)	0	(0)
Tachycardia	2	(2)	2	(2)	2	(1)	5	(4)
Agitation	2	(2)	2	(2)	2	(1)	2	(2)
Anxiety	2	(2)	0	(0)	2	(1)	0	(0)
General pain	2	(2)	0	(0)	2	(1)	0	(0)
Hyperhidrosis	2	(2)	6	(6)	2	(1)	6	(5)
Upper respiratory disorder	2	(2)	1	(1)	2	(1)	1	(1)
Complications of medical care§	1	(1)	0	(0)	2	(1)	1	(1)
Total number of clinical events	99		92		128		128	
Number of patients with clinical events	50	(56)	48	(52)	68	(52)	67	(51)
Number of patients enrolled	90		93		130		132	

Includes events reported for at least 1% of fenoldopam-treated patients in COMBINED DATA set. Rank ordered based on COMBINED DATA set.

* Totals include 18 patients in study 142 who received both fenoldopam and nitroprusside. Clinical events are listed according to the medication received at the onset of the event.

\+ The dictionary preferred term "Hypotension" includes only reductions in blood pressure specifically designated as hypotensive by the investigator.

§ The dictionary preferred term "Complication of medical care" includes clinical events relating to complications of catheter placement, namely, "Fenoldopam infusion infiltrated" and "I.V. nitroprusside was infiltrated".

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On-Therapy AEs for Subjects receiving IV Fenoldopam

A total of 184 AEs were reported in 45% subjects as follows (sponsor's Table 4.17).

Number AEs for Subjects

Body System	Number Subjects (N=204)		Number Events
Cardiovascular	57	28%	73
Digestive	7	3%	7
General Body	41	20%	51
Genitourinary	3	2%	3
Metabolic	2	1%	2
Musculoskeletal	1	<1%	1
Nervous	17	8%	17
Psychological	13	6%	17
Respiratory	13	6%	11
Total	91	45%	184

The most commonly reported events were flushing (25%), headache (15%), palpitations (7%), upper respiratory disorder (6%), nervousness (6%), dizziness (3%), malaise/fatigue (3%) and somnolence (2%).

On-Therapy AEs for All Patients, All Studies

AEs from all iv studies are presented in sponsor's Table 4.19.

Table 4.19: Rank-order of On-therapy Clinical Events* for All Patients Who Received Intravenous Fenoldopam (Appendix 4.1)

(n=598)

Clinical Event	Number of Patients	(%)
Headache	64	(11)
Flushing	41	(7)
Hypotension+	33	(6)
Nausea	30	(5)
Decreased serum potassium	23	(4)
Ventricular extrasystoles	17	(3)
Abnormal ECG§	17	(3)
Vomiting	15	(3)
Dizziness	15	(3)
Blood pressure decreased+	10	(2)
Tachycardia	9	(2)
Limb cramp	8	(1)
Insomnia	8	(1)
Dyspnea	7	(1)
Upper respiratory disorder	7	(1)
Complication of medical care¶	6	(1)
Anxiety	6	(1)
Nausea and vomiting	6	(1)
Total number of clinical events	471	
Total number of patients with clinical events	263	(44)

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Evaluation of Blood Pressure and Heart Rate - In Studies

In the interval studies, only two patients had either blood pressure or heart rates of concern associated with withdrawal of medication.

In the combined database, data from 320 patients were evaluated. Six patients had blood pressures or heart rates of concern (< 60 mm Hg DBP and/or < 100 mm Hg SBP; HR > 120 bpm or < 60 bpm). In the comparative studies with nitroprusside, there was no difference between treatments. Ten/320 had BP readings of concern, 4 associated with AEs requiring withdrawal from the study. There were 34/320 with HRs > 120 bpm; majority (68%) were tachycardic at baseline and two had associated events, one being withdrawn.

There were 31 with HRs < 60 bpm, one being withdrawn due to AEs.

Post-therapy, there were 18/301 with BPs of concern, 5 with AEs. A total of 11 had HRs > 120 bpm; one was associated with atrial fibrillation. Sixty three had HRs < 60 bpm, with two having serious bradycardia and one sinus arrhythmia.

Blood Pressure and HR for Patients in All Hypertension Trials

In all studies, there were 384 patients (320 severe hypertensives). Of the severe hypertensives, 8 had DBP < 60 mm Hg, 6 had SBP < 100 mm Hg, 34 had HR > 120 bpm and 31 had HR < 60 bpm. The corresponding numbers for the 64 mild/moderate hypertensives were 2, 0, 1, 19, respectively.

In the severe hypertension studies, the numbers with values of concern on- or post-therapy are presented below (sponsor's Table 5.2).

Number of Patients with One or More Vital Signs of Concern

Vital Sign	On-Therapy		Post-Therapy	
DBP < 60 mm Hg	8/320	3%	11/301	4%
SBP < 100 mm Hg	6/320	2%	12/301	4%
DBP < 60 and SBP < 100*	4/320	1%	5/301	2%
HR > 120 bpm	34/320	11%	11/301	4%
HR < 60 bpm	31/320	10%	63/301	21%

* The patients in this group are also included in the groups of < 60 or < 100 mm Hg.

A total of 10 patients had BP of concern, 4 with DBP < 60 mm Hg, 2 SBP < 100 mm Hg and 4 had both DBP and SBP of concern. Seven/10 had AEs of hypotension or dizziness associated with the low BPs. Four were withdrawn from the studies, one had infusion temporarily stopped and for two infusion rate was decreased.

Post-therapy, 18/301 had BPs of concern. Six had DBP < 60 mm Hg, 7 had SBP < 100 mm Hg and 5 had both values of concern. Five had associated AEs.

There were 34/320 with at least one HR > 120 bpm during infusion and 11 post-infusion. Of the 34 on-therapy, 22 had baseline HRs > 100 bpm, 6 between 90-99 and 6 between 80-89 bpm. Only two had AEs reported, one being withdrawn from study.

Post-therapy, 11 patients had HRs > 120 bpm and 7 of these had baselines > 100 bpm and all had HRs > 100 bpm during infusion. Maximum HRs ranged from 125 to 148 bpm. Only one had associated AE.

There were 31/320 patients with HRs < 60 bpm on therapy and 63 post-therapy. Of the 31 on-therapy, 26 had minimum HR 50-59 bpm. Only one had AE. Post-therapy, 63 had HRs < 60 bpm, 58 within range 50-59 bpm. At least 51 were receiving other antihypertensives, including beta-blockers during this period. AEs were reported for 3/63, 2 bradycardias and one sinus arrhythmia.

Blood Pressure and Heart Rate in Controlled Studies

Values of concern were compared for fenoldopam (n=117) and nitroprusside (n=119). On-therapy 1/117 fenoldopam and 5/119 nitroprusside patients had DBP < 60 mm Hg, and post-therapy numbers were 8/115 and 7/117, respectively. For SBP < 100 mm Hg, the respective numbers were 2/117 and 3/119 on-therapy and 6/115 and 5/117 post-therapy.

Heart rates > 120 bpm were seen in 18/117 fenoldopam and 17/119 nitroprusside patients on-therapy and 5/115 and 5/116, respectively post-therapy. The numbers with HRs < 60 bpm were 7/117 and 21/119, respectively on-therapy and 21/115 and 31/116 respectively, post-therapy.

AEs Associated with Vital Signs of Concern Resulting in Withdrawal from Infusion

In the interval studies, one fenoldopam and two nitroprusside patients were withdrawn due to AEs associated with vital signs of concern. In the combined data, there were no additional withdrawals.

Evaluations of ECGs

Atrial Rate, Ventricular Rate and ECG Intervals

Sponsor only discusses the two interval studies and not the combined data.

The parameters evaluated were atrial rate, ventricular rate, PR, QRS and QTc intervals. The baseline values and changes for both studies are shown in sponsor's Tables 6.1 - 6.4.

In protocol A52, sponsor states that there were no worsening of abnormalities that were present at baseline. (Data not available to reviewer). One patient developed PVCs and, from 7 hours to end of infusion, one patient had improvement in abnormal T waves and two had improvements in nonspecific ST segment changes. Post-therapy, 7 had T wave abnormalities, nonspecific ST changes and nonspecific PVCs.

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Table 6.1: Average Change from Baseline (± SD) for Atrial Rate, Ventricular Rate, PR Interval, QRS Interval, and QTc Interval On-therapy for Fenoldopam Patients in A52 (Appendix 6.1)

	Baseline	---Average Change from Baseline--- 0-7 Hours On-therapy	7 Hours On-Therapy to End of Infusion
Atrial rate (bpm)	80.6 ± 4.0 (n=18)	5.4 ± 3.5 (n=16)	0.8 ± 3.3 (n=10)
Ventricular rate (bpm)	80.6 ± 4.0 (n=18)	5.4 ± 3.5 (n=16)	0.8 ± 3.3 (n=10)
PR interval (msec)	156.7 ± 4.1 (n=18)	2.7 ± 3.3 (n=15)	2.0 ± 3.6 (n=10)
QRS interval (msec)	69.8 ± 4.9 (n=18)	4.6 ± 3.0 (n=16)	14.4 ± 10.5 (n=10)
QTc interval (msec)	372.3 ± 13.4 (n=15)	4.8 ± 6.3 (n=15)	-1.5 ± 6.1 (n=10)

Table 6.2: Average Change from Baseline (± SE) for Atrial Rate, Ventricular Rate, PR Interval, QRS Interval, and QTc Interval On-therapy for Fenoldopam Patients in D1101 (Appendix 6.1)

	Baseline	Average Change from Baseline 6 Hours On-Maintenance
Atrial rate (bpm)	87.5 ± 2.1 (n=83)	0.8 ± 1.8 (n=67)
Ventricular rate (bpm)	87.4 ± 2.0 (n=84)	0.8 ± 1.8 (n=68)
PR interval (msec)	160.0 ± 3.2 (n=83)	0.1 ± 2.4 (n=67)
QRS interval (msec)	122.1 ± 18.5 (n=84)	-1.8 ± 3.3 (n=68)
QTc interval (msec)	437.1 ± 6.4 (n=83)	9.5 ± 4.3 (n=68)

Table 6.3: Average Change from Baseline (± SE) for Atrial Rate, Ventricular Rate, PR Interval, QRS Interval, and QTc Interval Post-therapy for Fenoldopam Patients in A52 (Appendix 6.1)

	Baseline	Average Change from Baseline Within 48 Hours Post-therapy
Atrial rate (bpm)	80.6 ± 4.0 (n=18)	-4.6 ± 2.6 (n=118)
Ventricular rate (bpm)	80.6 ± 4.0 (n=18)	-4.6 ± 2.6 (n=18)
PR interval (msec)	156.7 ± 4.1 (n=18)	-3.3 ± 6.0 (n=18)
QRS interval (msec)	69.8 ± 4.9 (n=18)	3.6 ± 2.5 (n=18)
QTc interval (msec)	372.3 ± 13.4 (n=15)	12.5 ± 7.0 (n=15)

Table 6.4: Average Change from Baseline (± SE) for Atrial Rate, Ventricular Rate, PR Interval, QRS Interval, and QTc Interval Post-therapy for Fenoldopam Patients in D1101 (Appendix 6.1)

	Baseline	-Average Change from Baseline- 24 Hours Post-therapy	48 Hours Post-therapy
Atrial rate (bpm)	87.5 ± 2.1 (n=83)	-6.8 ± 1.8 (n=71)	-9.7 ± 2.0 (n=80)
Ventricular rate (bpm)	87.4 ± 2.0 (n=84)	-6.7 ± 1.8 (n=72)	-9.5 ± 1.9 (n=81)
PR interval (msec)	160.0 ± 3.2 (n=83)	2.5 ± 2.3 (n=71)	1.8 ± 2.7 (n=80)
QRS interval (msec)	122.1 ± 18.5 (n=84)	-12.2 ± 11.1 (n=72)	1.0 ± 1.8 (n=81)
QTc interval (msec)	437.1 ± 6.4 (n=83)	-3.0 ± 6.7 (n=71)	-11.7 ± 4.3 (n=80)

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In 0110l, there were T wave and ST segment changes. Eight patients experienced T wave changes that were not present at baseline or worsening of a previous abnormality. These occurred in 4% with T wave abnormalities at baseline and in 16% without baseline changes.

Overall combined data are not discussed, but it is the reviewer's recollection that there were changes in ECG parameters in the original NDA and that these had been specifically mentioned in the review.

Withdrawals for Clinical Events

In the interval studies, 24 patients were withdrawn for AEs (11 fenoldopam). Of 802 patients and subjects who had received fenoldopam, 42 (5%) were withdrawn for AEs.

In 11 studies, patients were withdrawn mainly for cardiovascular and digestive reasons. The number of patients withdrawn, by body system, is shown in sponsor's Table 7.1.

Table 7.1: Number* and Percentage of Fenoldopam Patients Withdrawn for Clinical Events from Intravenous Studies (Appendix 7.1)

	Number of Patients					
Body System	Severe Hypertension (n=112)#	(%)	Hypertension (n=384)##	(%)	Non-hypertension (n=75)	(%)
Cardiovascular	7	(6)	19	(5)	0	(0)
General body	2	(2)	8	(2)	1**	(0)
Nervous	2	(2)	6	(1)	0	(0)
Digestive	7	(6)	9	(2)	0	(0)
Integumentary	0	(0)	0	(0)	0	(0)
Metabolic	3	(3)	4	(1)	0	(0)
Psychological	1	(1)	1	(<1)	0	(0)
Patients withdrawn	11	(10)	28	(7)	1	(1)

* Numbers are not additive because some patients had clinical events in more than one body system at time of withdrawal.
**Represents patient with abdomino-pelvic pain.
Fenoldopam treated patients in INTERVAL STUDIES.
##All hypertension patients to date receiving intravenous fenoldopam.

The more commonly reported events resulting in withdrawal were [illegible]: vomiting 4, hypotension 4, decreased blood pressure 3, nausea 3, nervousness 2. One/75 in non-hypertension studies was withdrawn due to abdominal pain.

Deaths

Since the submission of the 120 day update, one CHF patient died of ventricular fibrillation. This was considered possibly fenoldopam related. Four patients died within 30 days post-therapy, all considered unrelated to drug. There were 21 deaths with oral drug, 18 unrelated to medication and 3 possibly related. An additional 11 died within 30 days post-therapy.

Total experience to date, one died on-therapy, 10 within 30 days. With oral formulation, 72 (70 CHF) died on-therapy, majority (79%) after 30 days therapy; 20 died within 30 days post-therapy.

In hypertension studies, one patient died 8 days post-therapy of aortic dissection. Majority of deaths occurred in non-hypertension studies. Three post-therapy deaths occurred, 6 hours, 3 days and 14 days post-therapy. The causes of death were cardiogenic shock/edema, possible pulmonary embolism and worsening CHF. All were considered unrelated to drug.

Of the 70 deaths in total experience, 57 were due to primary disease. The balance were due to pulmonary edema, pulmonary infection, pneumonia, cerebral-embolic event, subdural hematoma, stroke, cerebrovascular accident, urosepsis, suicide, liver cancer.

Time on Therapy for CHF Patients at Time of Death

Since 120-day update.

One patient died after 21 days therapy due to possible arrhythmia.

Table 9.2: Number and Percentage of Patients in Intravenous Severe Hypertension Studies with Hematology Test Values of Sponsor-defined Concern or with a Change from Baseline of Sponsor-defined Concern (Appendixes 9.2 and 9.2A)

Laboratory test	Baseline	(%)	On-therapy	(%)	Post-therapy 1-2 days	(%)	Post-therapy 3-20 days	(%)
Hemoglobin								
<80% lower limit normal								
INTERVAL DATA:	7/111	(6)	4/79	(5)	9/106	(8)	4/33	(12)
COMBINED DATA:	9/316	(3)	4/79	(5)	20/282	(7)	9/190	(5)
>120% upper limit normal								
INTERVAL DATA:	0/111	(0)	0/79	(0)	0/106	(0)	0/33	(0)
COMBINED DATA:	1/316	(<1)	0/79	(0)	0/282	(0)	0/190	(0)
-25% change								
INTERVAL DATA:	--		0/78	(0)	1/106	(1)	2/32	(6)
COMBINED DATA:			0/78	(0)	6/279	(2)	4/188	(2)
-25% change								
INTERVAL DATA:	--		0/78	(0)	0/106	(0)	0/33	(0)
COMBINED DATA:			0/78	(0)	0/279	(0)	1/188	(<1)
Total neutrophils								
~~<1.5 x 10^3/mm^3~~								
INTERVAL DATA:	0/103	(0)	0/76	(0)	0/99	(0)	0/32	(0)
COMBINED DATA:	1/276	(<1)	1/76	(1)	3/243	(1)	3/160	(2)
-20% change								
INTERVAL DATA:	--		12/72	(17)	34/95	(36)	12/31	(39)
COMBINED DATA:			12/72	(17)	77/231	(33)	52/152	(34)
WBC								
<3 x 10^3/mm^3								
INTERVAL DATA:	0/111	(0)	0/79	(0)	0/106	(0)	0/33	(0)
COMBINED DATA:	0/317	(0)	0/79	(0)	1/282	(<1)	0/188	(0)
>20 x 10^3/mm^3								
INTERVAL DATA:	0/111	(0)	0/79	(0)	0/106	(0)	2/33	(6)
COMBINED DATA:	1/317	(<1)	0/79	(0)	1/282	(<1)	3/188	(2)
-25% change								
INTERVAL DATA:	--		4/78	(5)	15/106	(14)	8/32	(25)
COMBINED DATA:			4/78	(5)	35/280	(13)	32/186	(17)
+25% change								
INTERVAL DATA:	--		20/78	(26)	20/106	(19)	6/32	(19)
COMBINED DATA:			20/78	(26)	46/280	(16)	22/186	(12)
Platelets								
~~<100 x 10^3/mm^3~~								
INTERVAL DATA:	2/111	(2)	1/79	(1)	2/104	(2)	1/32	(3)
COMBINED DATA:	2/293	(1)	1/79	(1)	5/271	(2)	1/161	(<1)
-20% change								
INTERVAL DATA:	--		5/78	(6)	7/104	(7)	3/31	(10)
COMBINED DATA:			5/78	(6)	24/262	(9)	11/155	(7)

• Percentages for change from baseline are calculated based on the number of patients with a post-therapy value who also had a baseline value.

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On-Therap. Deaths CHF Patients by Time on Fenoldopam (Sponsor's Table 3.)

Time on Drug (Days)	Since Submission of 120 Day Update N=19		Total Experience N=70	
	Number Deaths	Possibly Related	Number Deaths	Possibly Related
1 or less	0	0	1	1
2 to 7	0	0	2	1
8 to 30	1	0	14	3
> 30	18	3	53	6
Mean time on Fenoldopam	424 days		214 days	

Post therap. Deaths in CHF

Since 120 day update, six patients died in the studies while receiving medication other than fenoldopam. Three received captopril (primary disease, subdural hematoma, unknown); one Moduretic 9primary disease) and 2 placebo (primary disease, upper GI bleed).

For total experience, 18 died on-therapy receiving other treatment. Ten received captopril (6 primary disease, 1 subdural hematoma, 3 unknown); one Moduretic (primary disease); 7 placebo 9primary 6,1 upper GI bleed).

In chronic renal failure, 2 patients died since 120 Day report, both from cardiovascular causes: cardiac arrest after 417 days treatment and MI after 264 days. Post therapy, there was 1 death, worsening CHF.

Clinical Laboratory Evaluations

Summary IV Fenoldopam

Sponsor states that there were no significant safety issues associated with any lab trends. The most common abnormalities were elevated renal function tests, which sponsor feels were due to the effect of the hypertension on the kidney. There were decreases in total neutrophil values in some studies. In CHF studies, decreases in platelet counts and increases in the number of patients with values below normal, were found.

Review

In the interval studies, changes in renal parameters were noted as well as decreased hematocrit, hemoglobin, RBC count and neutrophils.

Combined data from 320 severe hypertensives, presented no major lab abnormalities. Certain changes were probably due to the primary disease state, except possibly the renal changes.

The number of patients with hematology changes of concern are summarized in sponsor's Table 9.2 and number with values outside normal range in 9.3.

Table 9.3: Number and Percentage of Patients in Intravenous Severe Hypertension Studies with Values Outside the Normal Range for Selected Hematology Tests (H=High; L=Low) (Appendixes 9.4 and 9.4A)

Laboratory Test	Baseline (%)	On-therapy (%)	-------Post-therapy----- 1-2 days (%)	3-20 Days (%)
Hematocrit (L)				
INTERVAL DATA:	23/111 (21)	25/79 (32)	33/106 (22)	6/33 (18)
COMBINED DATA:	71/318 (22)	25/79 (32)	92/282 (33)	50/190 (26)
Hemoglobin (L)				
INTERVAL DATA:	20/111 (18)	22/79 (28)	34/116 (29)	7/33 (18)
COMBINED DATA:	64/316 (20)	22/79 (28)	93/282 (33)	50/190 (26)
Red blood cells (L)				
INTERVAL DATA:	16/110 (15)	16/79 (20)	29/106 (27)	5/33 (15)
COMBINED DATA:	50/301 (17)	16/79 (20)	74/280 (26)	43/175 (25)
Total neutrophils (L)				
INTERVAL DATA:	9/103 (9)	6/76 (8)	12/99 (12)	3/32 (9)
COMBINED DATA:	15/276 (5)	6/76 (8)	25/243 (10)	11/160 (7)
Platelets (L)				
INTERVAL DATA:	5/111 (5)	2/79 (3)	8/104 (5)	1/32 (3)
COMBINED DATA:	9/293 (3)	2/79 (3)	14/271 (5)	3/161 (2)
WBC (L)				
INTERVAL DATA:	5/111 (5)	5/79 (6)	7/106 (7)	2/33 (6)
COMBINED DATA:	19/317 (6)	5/79 (6)	27/282 (10)	14/188 (7)
WBC (H)				
INTERVAL DATA:	18/111 (16)	17/79 (22)	23/106 (22)	4/33 (12)
COMBINED DATA:	50/317 (16)	17/79 (22)	53/282 (19)	16/188 (9)

Serum electrolytes did not vary by much. Potassium values < 3 meq/L was seen in 4% at baseline, 8% on-therapy and 4% at 1-2 days post-therapy. About 3% had less than 25% change and 12% > 25% change on- and post-therapy. Electrolyte changes usually reversed within 3 to 20 days post-therapy. The number of patients with potassium values outside the normal range is summarized as follows:

Number of Patients with Potassium Values Outside Normal Range

Baseline		On-Therapy		1-2 Days Post		3-20 days Post	
LOW							
62/312	20%	103/273	38%	92/312	29%	13/211	6%
HIGH							
8/312	3%	7/273	3%	14/313	4%	3/211	1%

The number of patients with renal parameters above the normal range is presented in the next Table (sponsor's Table 9.7).

Number Patients with Renal Parameters Above Normal Range

Test	Baseline		On-Therapy		1-2 Days Post-		3-20 Days Post-	
BUN	56/245	23%	47/213	22%	110/244	45%	61/161	38%
Creatinine	106/316	34%	92/268	34%	144/313	46%	75/212	35%
Urea	22/56	39%	18/53	34%	26/54	48%	15/38	39%
Uric acid	62/218	28%	9/26	35%	67/190	35%	64/163	39%

The number of patients with values above normal for liver function tests were:

Number Patients with Values Above Normal for Liver Function Tests

Test	Baseline		On-Therapy		1-2 Days Post-		3-20 Days Post-	
Alk Phos	42/307	14%	12/78	15%	27/278	10%	14/187	7%
ALAT	58/294	20%	17/708	24%	56/260	22%	30/182	16%
ASAT	38/309	12%	14/79	18%	42/280	15%	23/192	12%
Total Bili	23/305	8%	10/78	13%	27/274	10%	2/185	1%

A significant number of patients showed abnormal values for urine bacteria, casts, crystals, epithelial cells, RBCs and WBCs. Sponsor feels that these changes were due to the primary disease effect on the kidney but this does not explain the increase on-therapy and subsequent decrease post-therapy. It appears that there is an effect on the kidney

Number Patients with Abnormal Values for Urinalysis

Test	Baseline		On-Therapy		1-2 Days Post-		3-20 Days Post-	
Bacteria	92/234	39%	75/171	44%	127/250	51%	56/152	37%
Casts	20/233	9%	29/168	17%	63/249	25%	23/150	15%
Crystals	16/225	7%	14/162	9%	49/240	20%	18/141	13%
Epith Cell	64/235	27%	43/171	25%	98/251	39%	43/150	29%
RBC/HPF	101/235	43%	84/171	49%	136/250	54%	52/154	34%
WBC/HPF	112/235	48%	67/172	39%	140/250	56%	72/153	47%

Lab Values in Non-Hypertension Studies

Sponsor only presents the results as values of "sponsor-defined concern" and not in relation to normal values. In CHF studies, there was a decrease in number of pletelets from baseline with 26% being below normal on-therapy (baseline 14% below normal), 21% at 1-2 days post- and 32% at 3-20 days post-therapy. The other results are best presented as sponsor's Tables 9.13 and 9.15.

Dose Response Data

The incidence of AEs increased with increased infusion rates. In the interval data, at rates < 0.1 mcg/kg/min, the AE incidence was 4% increasing to 19-29% at higher rates. Higher cumulative doses were also associated with higher incidence of events, 7-15% up to 0.149 mcg/kg and 28% at doses > 0.15 mg/kg. Nausea/vomiting occurs more frequently at higher infusion rates. In the combined database, it was found that flushing, headache and nausea/vomiting were all dose related.

At an infusion rate of < 0.1 mcg/kg/min, the incidence of AEs was 6%, increasing to 22% at 0.1-0.29, 20% at 0.3-0.49, 18% at 0.5-0.69, and 30% over this rate. The first onset of flushing occurs at lower infusion rates < 0.7 mcg/kg/min and at lower cumulative doses < 0.02 mg/kg. Headaches and vomiting occur more at higher rates (1.0 mcg/kg/min) and at higher cumulative doses of 0.149 mg/kg and higher. The AE incidence for cumulative doses parallels the infusion rate, being 8% at < 0.1 mg/kg rising to 13% at 0.1-0.19, then remaining steady until > 0.149 with an incidence of 29%.

The incidence of the most commonly reported AEs viz a viz infusion rates and cumulative dose is presented in sponsor's Tables 11.3 and 11.4.

Drug-Drug Interactions

The most commonly used concomitant medication was arteriolar smooth muscle relaxants (36% pre-therapy, 20% on-therapy and 54% post-). there was an increased incidence of flushing with pre-therapy alpha blockers (25%) compared to 4% with no antihypertensive and 19% with ACE inhibitors.

Headache was more frequent in patients who had received pre-therapy centrally acting anti-adrenergic agents and alpha blockers (25%). Frequency with other treatments was 8% with other antihypertensives to 15% ACE inhibitors. Patients who had not received previous antihypertensives did not experience headaches on-therapy.

Table 11.4
Number and Percentage of Patients with the Most Frequently (≥ 4%) Reported On-therapy Clinical Events in Severe Hypertension Studies by Fenoldopam Cumulative Dose (mg/kg) at First Onset

Appendices 11.3 and 11.3A

Patients Exposed	Total		CUMULATIVE DOSE OF IV FENOLDOPAM (mg/kg)													
			0-.009		.01-.019		.02-.029		.03-.059		.06-.089		.09-.119		.12-.149		≥.140	
INTERVAL	112		112		111		106		108		88		75		69		68	
COMBINED	320		320		305		285		268		203		159		126		109	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Headache																		
INTERVAL	17	(15)	-	(-)	3	(3)	1	(<1)	4	(4)	2	(2)	2	(3)	-	(-)	6	(9)
COMBINED	39	(12)	-	(-)	7	(2)	1	(<1)	12	(6)	7	(3)	2	(1)	1	(<1)	9	(8)
Nausea/Vomiting*																		
INTERVAL	15	(13)	-	(-)	5	(5)	-	(-)	2	(2)	1	(1)	1	(1)	3	(4)	3	(5)
COMBINED	28	(9)	-	(-)	5	(2)	2	(<1)	4	(2)	4	(2)	1	(<1)	4	(3)	8	(7)
Flushing																		
INTERVAL	7	(6)	1	(<1)	5	(5)	1	(<1)	-	(-)	-	(-)	-	(-)	-	(-)	-	( )
COMBINED	38	(9)	9	(3)	13	(4)	4	(1)	3	(1)	1	(<1)	-	(-)	-	(-)	-	(-)
Decreased K																		
INTERVAL	7	(6)	-	(-)	1	(<1)	-	(-)	1	(1)	1	(1)	2	(3)	-	(-)	2	(3)
COMBINED	18	(5)	-	(-)	2	(<1)	-	(-)	1	(<1)	2	(1)	5	(3)	-	(-)	6	(6)
Vent. Extrasys.																		
INTERVAL	4	(4)	-	(-)	1	(<1)	2	(2)	-	(-)	-	(-)	1	(1)	-	(-)	-	(-)
COMBINED	14	(4)	5	(2)	5	(2)	2	(<1)	1	(<1)	-	(-)	1	(<1)	-	(-)	-	(-)
Dizziness																		
INTERVAL	4	(4)	-	(-)	2	(2)	1	(<1)	-	(-)	-	(-)	-	(-)	-	(-)	1	(2)
COMBINED	13	(4)	2	(<1)	4	(1)	4	(1)	1	<1)	-	(-)	1	(<1)	-	(-)	1	(<1)
Hypotension																		
INTERVAL	4	(4)	1	(<1)	1	(<1)	-	(-)	1	(1)	-	(-)	1	(1)	-	(-)	1	(2)
COMBINED	14	(4)	2	(<1)	2	(<1)	3	(1)	4	(2)	-	(-)	1	(<1)	1	(<1)	1	(<1)

Key: Vent. Extrasys. = Ventricular extrasystoles; K = potassium; dizziness includes giddiness and postural dizziness in one patient at 1.0 - 1.5 rate.
* Nausea, vomiting and nausea with vomiting

Blacks had a higher incidence of post-therapy events than did non-blacks (45% vs 21%), especially headache.

In the combined data, 80% of patients had received prior medications, especially arteriolar smooth muscle relaxants, central anti-adrenergics, ACE inhibitors and beta-blockers and diuretics. During the study, 53% received concomitant medications and 88% post-infusion. The incidence of AEs by drug category were:

Percentage Patients with On-Therapy AEs, by Drug Group

Drug Group	Number of Patients	Percentage
Alpha Blockers	15/24	63
ACE inhibitors	38/67	57
Central anti-adrenergic	37/63	59
Diuretics	62/115	54
Beta-Blockers	30/62	48
Other antihypertensives	23/53	43
Calcium channel blockers	32/68	47
No antihypertensive	53/120	44

The most commonly reported events were flushing, reported with all groups of drugs except other antihypertensive group. This was most common with alpha blockers (25%), beta-blockers and ACE inhibitors (19%). Headache was reported by 25% with alpha blockers and 25% centrally acting anti-adrenergics. This was not reported in Other antihypertensive group. Nausea/vomiting was mainly with calcium blockers (29%) and beta-blockers (27%) in the interval studies but 4-10% for all groups in combined data.

Post-Therapy AEs

The incidence of events post-therapy by drug group is shown in sponsor's Table 12.3.

Percentage Patients with Post-Therapy AEs, by Drug Group

Drug Group	Number of Patients	Percentage
Other antihypertensives	33/54	61
Diuretics	59/121	49
Central anti-adrenergic	37/85	44
Alpha Blockers	25/61	41
Beta-Blockers	21/58	36
Calcium channel blockers	47/132	36
ACE inhibitors	36/100	36
No antihypertensive	3/62	5

There were no reports of flushing in any group. Headache was reported in all groups except in the no antihypertensive group. Incidence of headache was 5% beta blockers to 19% other antihypertensives. Nausea/vomiting occurred 1% with calcium blockers and central anti-adrenergics to 9% with other antihypertensives. No nausea/vomiting was reported in the no antihypertensive group.

More blacks than non-blacks 45% vs 31%, had post-therapy events in all groups except ACE inhibitors where the incidence was the same.

Drug Demographic Interactions

Age

In the interval data, the incidence of AEs was lower in the > 65 year group than in < 65 years (44% vs 55%). In the combined data, the incidence was the same. Nausea/vomiting was more frequent in the younger group. The breakdown of patients by age and body system in seen in sponsor's Table 13.1.

Table 13.1: Number and Percentage of Patients with On-therapy Clinical Events Grouped by Age (Appendix 13.3, 13.3.A)

	Less Than or Equal to 65 Years		Greater Than 65 Years	
		(%)		(%)
Cardiovascular				
INTERVAL DATA:	24	(23)	2	(22)
COMBINED DATA:	70	(24)	6	(19)
Digestive				
INTERVAL DATA:	14	(14)	1	(11)
COMBINED DATA:	27	(9)	1	(3)
General body				
INTERVAL DATA:	24	(23)	1	(11)
COMBINED DATA:	51	(18)	5	(16)
Genitourinary				
INTERVAL DATA:	2	(2)	0	(0)
COMBINED DATA:	8	(3)	1	(3)
Hematic				
INTERVAL DATA:	2	(2)	0	(0)
COMBINED DATA:	3	(1)	0	(0)
Integumentary				
INTERVAL DATA:	4	(4)	0	(0)
COMBINED DATA:	6	(2)	0	(0)
Metabolic				
INTERVAL DATA:	10	(10)	0	(0)
COMBINED DATA:	19	(7)	2	(6)
Musculoskeletal				
INTERVAL DATA:	3	(3)	0	(0)
COMBINED DATA:	8	(3)	0	(0)
Nervous				
INTERVAL DATA:	11	(11)	1	(11)
COMBINED DATA:	22	(8)	1	(3)
Psychological				
INTERVAL DATA:	4	(4)	1	(11)
COMBINED DATA:	7	(2)	1	(3)
Respiratory				
INTERVAL DATA:	4	(4)	1	(11)
COMBINED DATA:	9	(3)	1	(3)
Number of patients with at least one clinical event				
INTERVAL DATA:	57	(55)	4	(44)
COMBINED DATA:	141	(49)	14	(45)
Number of patients receiving fenoldopam				
INTERVAL DATA:	103	(100)	9	(100)
COMBINED DATA:	289	(100)	31	(100)

Post-therapy, only one/9 over 65 years had an AE compared to 24/100 < 65 years in the interval data. In combined data, 8/21 > 65 years had AEs compared to 97/289 less than 65 years. Within body systems, older patients had more cardiovascular events 13% vs 8%, while younger group had more general body symptoms (10% vs 3%), and hematic (5% vs 0%). Headache was more frequent in younger group (8% vs 3%). The major differences between the two groups were (number of patients with AEs):

	< 65 years		> 65 years	
Cardiovascular	24	8%	4	13%
Digestive	12	4%	1	3%
General Body	28	10%	1	3%
Genitourinary	11	4%	2	6%
Hematic	15	5%	0	0%
Metabolic	19	7%	2	6%
Nervous	21	7%	1	3%

Race

On-therapy events, by race, are summarized in the next Table.

Number of Patients On-Therapy AEs by Race

	Black		Caucasian		Other	
Cardiovascular	36	22%	38	25%	2	40%
Digestive	15	9%	13	8%	0	0%
General Body	39	19%	25	16%	1	20%
Genitourinary	6	4%	3	2%	0	0%
Hematic	2	1%	1	1%	0	0%
Integumentary	2	1%	4	3%	0	0%
Metabolic	14	9%	7	4%	0	0%
Musculoskeletal	6	4%	2	1%	0	0%
Nervous	10	6%	13	8%	0	0%
Respiratory	4	2%	6	4%	0	0%
TOTAL	83	52%	69	45%	3	60%

Post-therapy, interval data, had 28% blacks with AEs compared to 16% whites. The major difference was for headache 9% vs 4%. In the combined data, 45% reported events compared to 22% whites. Breakdown by body system is presented below.

Number of Patients Post-Therapy AEs by Race

	Black		Caucasian		Other	
Cardiovascular	14	9%	14	9%	0	0%
Digestive	9	6%	4	3%	0	0%
General Body	22	14%	7	4%	0	0%
Genitourinary	11	7%	2	1%	0	0%
Hematic	13	8%	2	1%	0	0%
Metabolic	17	11%	4	3%	0	0%
Musculoskeletal	2	1%	0	0%	0	0%
Nervous	14	9%	8	5%	0	0%
Respiratory	3	2%	0	0%	0	0%
TOTAL	72	45%	34	22%	0	0%

Sex

Interval data had 60% females reporting AEs compared to 49% males, especially cardiovascular, general body system, digestive and nervous. In the combined data, the ratio was 54% vs 42%. data are presented below.

Number of Patients On-Therapy AEs by Sex

	Females		Males	
Cardiovascular	38	27%	38	21%
Digestive	14	10%	14	8%
General Body	31	22%	25	14%
Genitourinary	1	1%	8	4%
Hematic	3	2%	0	0%
Integumentary	2	1%	4	2%
Metabolic	12	8%	9	5%
Musculoskeletal	3	2%	5	3%
Nervous	13	9%	10	6%
Respiratory	4	3%	6	3%
TOTAL	76	54%	79	44%

Females reported headaches more often than men (20% vs 10%).

Post-therapy AEs were reported by 32% females vs 34% males with no difference in events by body system. Abnormal WBC was reported in 4% males and 0% in females.

Drug-Disease Interaction

Secondary diagnoses included CHF (9%), diabetes (12%), renal failure (9%) and renal artery stenosis (3%). In the interval data, the percentage of patients with CHF (82%), diabetes (69%) and renal failure (59%) with AEs was higher than in the general population (54%). In the combined data, the respective percentages were CHF (59%), diabetes (58%), renal failure

(60%) and general population (48%). The most frequent event was headache (± 25%).

In the post-therapy phase, AEs were higher for diabetics in the interval data (54%) compared to CHF (36%) and total group (22%). In the combined database, the percentage AEs were similar in all cases (30-40%). Headache was the most common event.

AEs from Other Sources

Individual investigators conducted additional tests and, it was found, that there was an increase in intraocular pressure of 3-4 mm Hg. (the reviewer has commented on this in a previous submission to the Agency).

Safety Update

The sponsor has a small section update from June 14, 1990 to July 31, 1990.

There were no deaths on-therapy but two deaths within 30 days post-therapy in acute renal failure studies. Both occurred within 10 days of termination of infusion. Causes of death was MI and central cardiovascular failure.

COMMENTS

1 There are no major new events reported that were not noted in the NDA

2 It was not always easy to cross-check data as the Table numbers cited in the text often did not correspond to the Table mentioned.

3 It was often difficult to balance numbers in the text with those in the appendices

4 As with the original NDA, this submission was not user friendly

5 There does not appear to be any major safety problems defined in this update.

20 Feb '97- last revised

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Food and Drug Administration

Division of Cardio-Renal Drugs
Tel 301-5945377; FAX-5495

Medical Review of NDA Studies

General information

NDA #:	**19-922**
Drug:	**Fenoldopam mesylate (Corlopam®)**
Sponsor:	Neurex Corporation
Proposed indication:	
related IND:	22-839
Date of NDA submission:	21 June 1996

Table of Contents:

1 Clinical Pharmacology studies

1.1 Renal and Neurohormonal Effects in Healthy Subjects (study A-49)

Design Summary

This baseline placebo-controlled, open-label, dose-ranging, drug-drug interaction study nonrandomly assigned 10 healthy subjects (after a single pre-treatment infusion of placebo) to receive (on separate days) 4 hour[1] iv infusions of fenoldopam (given as ascending 0.05, 0.10, 0.25, and 0.50 µg/kg/min doses in each subject) in the absence and presence of the dopaminergic antagonist, metoclopramide (10 mg/hr iv). On the evening before each of these 3 days (the placebo baseline day, the fenoldopam monotherapy day, and the fenoldopam-metoclopramide cotherapy day) all subjects were administered oral (300 mg) and potassium iodide (10 drops of "saturated" solution). Seven subjects participated in a subsequent study day in which lithium pre-treatment was withheld before a fenoldopam monotherapy infusion otherwise identical to study day 2. The objectives were to assess safety, and to estimate the influence of the various co-therapies on fenoldopam-mediated changes in renal hemodynamics (radioiothalamate-estimated glomerular filtration rate (GFR), radiohippurate-estimated effective renal plasma flow (ERPF), filtration fraction (FF)), sodium excretion, plasma renin activity and plasma aldosterone concentration.

Pharmacodynamic Outcomes

The sponsor provided no raw data, but only a brief summary report of their interpretation of results from this study. Reportedly, fenoldopam caused a dose-related (and metoclopramide-insensitive) increase from pre-treatment ERPF without changing GFR. At an unspecified time during fenoldopam infusions there were said to be 10 mm Hg (presumably mean) reductions in DBP which were reportedly antagonized (to an unspecified extent) by metoclopramide, no (presumably mean) change in SBP, and 2-fold increases from pre-treatment levels of plasma renin activity.

Safety Outcomes

See the section 3 below for a discussion of safety data from this study.

1.2 Effect on PEEP-induced Renal Dysfunction (study B-1404)

Design Summary

This uncontrolled, open-label study nonrandomly assigned 34 subjects (patients with positive end expiratory pressure (PEEP) ventilation-induced reduction in urine output of 25%) to receive a 4 hour iv infusion of fenoldopam (given for 2 hours at 0.1 µg/kg/min and uptitrated as tolerated to 0.2 µg/kg/min for 2 additional hours). Patients were to be maintained on constant fluid intakes. PEEP was begun at 4 cm H_2O and uptitrated to a maximum of 12 cm H_2O. The objectives were to assess safety and drug-associated changes from pre-drug measures of renal function (electrolyte and urine excretion, and creatinine clearance), peripheral hemodynamics, pulmonary function, and safety

[1] presumably the total daily exposure to any fenoldopam dose, but this is unclear.

in patients subjected to the renal effects of PEEP[2].

Investigative sites

The study's investigative sites were as follows:

Table: 1

Investigative sites in Study B-1404

site #	*Principal Investigator*	*location*
1	Dr. Suter	Univeristy Hospital Geneva, Switzerland
2	Dr. Schuster	Stadt Karankenhaus Hildesheim, Germany
3	Dr. Hemmer	Centre Hospitalier Luxembourg

Enrollment criteria.

Adult (>18 years) patients were eligible for enrollment if they required mechanical ventilation with PEEP and manifested a PEEP-induced reduction of 25% from the pre-PEEP level of urine output.

Excluded from enrollment were pregnant or lactating women as well as those subjects manifesting:

- recent use or the requirement for uninterrupted use of diuretics, dopamine, dopamine antagnosits, MAO inhibitors, vasodilators, or an investigational drug.
- uncontrollable ventricular dysrhythmia.
- chronic renal failure with serum creatinine >180 µmol/L or requiring dialysis.
- pheochromocytoma.
- thrombocytopenia.
- known hypersensitivity to sulphite, fenoldopam or related agents.
- hyponatremia.
- hypophosphatemia.

Endpoints.

The prespecified primary endpoints were reportedly the renal functional indices. Safety endpoints were as follows: observed adverse events (AE), hematology, and blood chemistry. All endpoint observations were obtained every 2 hours.

Statistical analysis.

Apparently "nonparametric tests for assessment of differences" were performed, but no further details were provided.

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[2]these are known to include decreases in GFR, natriuresis, and diuresis, and renal blood flow.

Pharmacodynamic Outcomes

The age of subjects ranged from 20-83 years. After stabilization of PEEP-associated changes, fenoldopam was associated with a 23 mL/min increase in mean urine flow after four hours of infusion.

PEEP was associated with a 115 *microEq*/min mean decrease from the pre-PEEP rate of potassium excretion. The subsequent fenoldopam infusion was associated with a relative increase above the PEEP-associated mean rate of potassium excretion of 9 microEq/min after two hours, and 27 microEq/min after four hours, but on-drug and immediated post-infusion values did not return to the pre-PEEP baseline[3].

There were apparently about 3 mm Hg fenoldopam-associated reductions in mean SBP, roughly 5-6 mm Hg reductions in mean DBP, about 6 bpm increases in mean HR, and little drug-associated change in pulmonary function indices.

Safety Outcomes

See section 3 below for discussion of safety data from this study.

1.3 **Hemodynamic effects in Congestive Heart Failure (study B-1214)**

Design Summary

This uncontrolled, open-label study nonrandomly assigned 9 subjects (NYHA class III-IV congestive heart failure (CHF) patients with left ventricular ejection fraction (LVEF) < 40%) to receive an iv fenoldopam infusion starting at 0.1 µg/kg/min and uptitrated until a 25% increase from pre-treatment CO or a dose rate of 2.5 mcg/kg/min was achieved, with maintenance of the highest achieved dose rate for up to 6 hours. The objectives were to assess safety, and central, peripheral and renal hemodynamics.

Pharmacodynamic Outcomes

The sponsor provided only an abbreviated report of the results of this study. The range of subject ages was 32-59 years. Reportedly, at the end of maintenance fenoldopam infusions the mean drug-associated changes from pre-treatment DBP[4], SBP, and HR were -13.9 mm Hg, -17.6 mm Hg, and 14.2 bpm, respectively.

Reportedly, CO was increased by at least 25% over pre-treatment values in all subjects, mean ERPF increased 193 ml/min over pre-treatment levels, and neither sodium excretion nor GFR changed to a clinically important extent in association with drug exposure.

Safety Outcomes

The sponsor's abbreviated report of the safety results of this study is reviewed in section 3 below.

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[3]as per the sponsor's table 14a, page 190, volume 57].

[4]postural positions were not described for any of these measurements.

1.4 Renal and hemodynamic effects in Edematous Chronic Renal Disease (study A-44):

Design Summary

This uncontrolled, open-label study nonrandomly assigned 27 subjects (chronic renal failure patients with edema despite loop diuretic treatment) to receive iv fenoldopam (titrated from 0.025 to 0.100 µg/kg/min) subsequent to a 24 hour washout of any previous antihypertensive medications. In phase I of the study 6 hour continuous iv fenoldopam infusions were started at 0.025 µg/kg/min for the first hour, and uptitrated every half hour by 0.010 µg/kg/min increments until a 100% increase over pre-treatment diuresis was achieved or a maximum doserate of 0.100 µg/kg/min was attained. The dose arrived at after 6 hours was maintained for an additional 6 hours (study phase II), and then an additional 18 hours. (study phase III). The objectives were to observe safety, diuresis, and systemic BPs in association with fenoldopam exposure.

Investigative sites

The study's investigative sites were as follows:

Table: 2

Investigative sites in Study A-44

site #	*Principal Investigator*	*location*
A	Dr. Rodicio	Madrid, Spain
B	Dr. Rof	Madrid, Spain

Enrollment criteria.

Adult patients (aged 18-70) were eligible for enrollment if they manifested stable chronic renal failure with GFR < 30 ml/min, daily diuresis < 700 mL during diuretic therapy, edema unresponsive to diuretics. Excluded from enrollment were pregnant women and women of childbearing potential as well as those subjects manifesting:

- congestive heart failure.
- diastolic BP ≥ 115 mm Hg.
- unstable angina, or myocardial infarction within the previous 3 months.
- hypertensive encephalopathy.
- SGOT, SGPT, or bilirubin values > 50% above upper limits of normal. - serum albumin < 2.5 gm/dL.
- history of vasculitis, collagen vascular disease, or immunomodulator use.
- requirement for the uninterrupted use of antihypertensives, diuretics, phenothiazine, or dopamine antagonists.

Pharmacodynamic Outcomes

The mean age of subjects was approximately 55 years. The final mean infusion rates ranged from approximately 0.07-0.09 µg/kg/min during the various phases of the study.

These pharmacodynamic analyses excluded one subject whose age was in excess of the enrollment criterion. Among 6 patients who were exposed to a 6 hour infusion reportedly the drug-associated peak mean increases from pre-treatment urine excretion (approximately 1.5 mL/min, occuring at around 2-3 hours post-dose) was statistically distinguishable, as were the mean decreases from pre-treatment SBP (approximately 12 mm Hg). DBP changes were not significant.

Among 10 patients exposed to a 12 hour infusion reportedly the drug-associated peak mean increase from pre-treatment urine excretion (approximately 0.5 mL/min) was statistically distinguishable, as were the decreases from pre-treatment SBP (approximately 20 mm Hg), and DBP (approximately 5 mm Hg).

Among 10 patients exposed to a 24 hour infusion the drug-associated peak mean increase from pre-treatment diuresis (approximately 1 mL/min) was reportedly statistically distinguishable, as were the decreases from pre-treatment SBP (approximately 10 mm Hg), and DBP (approximately 10 mm Hg).

Safety Outcomes

See section 3 below for a discussion of safety data from this study.

1.5 Renal and hemodynamic effects in Chronic Renal Failure Patients (study A-45):

Design Summary

This uncontrolled, open-label study nonrandomly assigned 12 subjects (chronic renal failure patients with GFR of 20-60 ml/min) to receive a brief iv fenoldopam infusion on day 1, followed by oral fenoldopam on days 2-11, and then another iv infusion on day 12. The day 1 infusion was for 2 hours (given as 0.05 µg/kg/min in the first five patients, and as 1 µg/kg/min in the rest), and oral

therapy began at 150 mg/d (in equally divided thrice-daily doses) during days 2-4, and was uptitrated to 300 mg/d (again, in equally divided thrice-daily doses) on days 5-11. The final day 12 iv fenoldopam infusion was at the same dose as given on day 1, and started 4.5 hours after the most recent oral dose. The objectives were to assess safety, and changes in renal hemodynamics (GFR, ERPF, FF), diuresis, and peripheral hemodynamics.

Investigative sites

The study's principal investigator was Dr. Donker of Vrije University, Amsterdam, The Netherlands.

Enrollment criteria.

Adult patients (aged 18-70) were eligible for enrollment if they manifested stable chronic renal failure with GFR between 20 and 60 ml/min. Excluded from enrollment were pregnant women and women of childbearing potential as well as those subjects manifesting:

- congestive heart failure requiring non-diuretic therapy.
- systolic BP below 95 mm Hg, or diastolic BP below 70 or above 95 mm Hg.
- unstable angina, or myocardial infarction within the previous 3 months.
- clinically significant dysrhythmias.
- SGOT, SGPT, or bilirubin values > 50% above upper limits of normal. - serum albumin < 2 gm/dL.
- hematuria.
- requirement for the uninterrupted use of antihypertensives, immunomodulators, monoamine oxidase inhibitors, catecholamines, cimetidine, NSAIDs, or dopamine antagonists.

Treatment regimen.

The daily protein and sodium intake of subjects was to be kept constant. Diuretics were to remain at unchanged doses. Nondiuretic anti-hypertensives were not allowed.

Drug preparations.

The tablet formulations were batch 5 for the 50 mg tablets and batch 35 for the 100 mg tablets. Parenteral fendoldopam was provided in 10 mg/mL ampules (batch 22F) which were diluted with 5% dextrose to achieve final concentrations of 1-100 µg/mL.

Endpoints.

There was no prespecification of a primary efficacy endpoint.

Statistical analysis.

The protocol specified that paired T-tests or Wilcoxon tests would be used to compare day 12 and day 1 GFR, ERPF, and BPs. All patients were included in the submitted efficacy analyses.

RESULTS:

Pre-treatment variables.

The subjects were 4 males and 8 females with a median age of 52.5 years, and a median pre-treatment GFR of 32 mL/min/1.73 m^2.

Pharmacodynamic Outcomes

Reportedly on day 1, immediately prior to iv infusion the mean values of urine excretion rate, ERPF, mean arterial BP, and HR were 4 ml/min, 141 ml/min/1.73 m^2, 105 mm Hg, and 65 bpm, respectively. The first iv fenoldopam infusion was reportedly associated with a statistically distinguishable 49% mean increase from pre-infusion urine flow, a 7% mean increase from pre-infusion ERPF were observed, no significant change observed in GFR or FF, a significant 4% reduction from pre-infusion mean arterial BP, and a significant 10% increase from pre-infusion HR.

After multi-doses the last oral dose was said to have been associated with a statistically significant 10% mean reduction from pre-dose arterial BP, and a trend towards a 7% mean reduction in HR (with pre-dose mean values of mean arterial BP, and HR reportedly being 105 mm Hg, and 77 bpm, respectively).

The final iv infusion reportedly was associated with a statistically distinguishable 22% mean increase from the 4 mL/min pre-infusion urine flow rate, but no significant change in ERPF, GFR or FF; a significant 2% reduction from the 101 mm Hg pre-infusion mean arterial BP was also reported, but no appreciable change from pre-infusion HR.

Safety Outcomes

See section 3 below for a discussion of safety data from this study.

2. Clinical efficacy trials

2.1 Steady-state pharmacokinetics/pharmacodynamics in essential hypertensives (study 94-5)

Design Summary

This double-blind[5], concurrent placebo-controlled and baseline placebo-controlled, parallel-group, pharmacokinetic/pharmacodynamic (PK/PD) study randomized 35 subjects (essential hypertension patients with untreated mean supine diastolic blood pressures (DBP) between 95 and 119 mmHg, but no evidence of end-organ damage) to receive a 48 hour iv infusion of placebo or fenoldopam (given as a fixed 0.04, 0.1, 0.4, or 0.8 µg/kg/min dose)[6]. Prior to randomization there was a 24 hour single-blind placebo lead-in (Day 1), and the lead-in was preceded by a 10 day washout of previous antihypertensive medications. After 2 days of randomized study drug infusion there was a 24 hour, single-blind, study drug withdrawal phase (on Day 4) during which placebo was administered. The principal measured parameters were systemic arterial blood pressure (BP), heartrate (HR), and plasma concentration of both parent drug (including assay for enantiomers) and

[5]the research pharmacist was unblinded, to allow for preparation of the correct dilution of study medication (given that drug was supplied in a solution of fixed concentration to be adminstered at a fixed infusion rate).

[6]one additional subject was erroneously administered a 0.01 µg/kg/min dose.

metabolites. The objectives were to assess PK/PD relationships, characterize maximally tolerated and minimally effective doses, and to observe for any evidence of tolerance or rebound.

The temporal sequence of phases in this study was as follows:

Table: 3

Temporal sequence of the phases of study 94-5

Days "minus 10 to 0"	*Day "1"*	*Days "2->3"*	*Day "4"*
pre-study medication washout	placebo run-in	randomized study drug infusion	study drug withdrawal (placebo given)

Investigative sites

The study's investigative sites were as follows:

Table: 4

Investigative sites in Study 94-5

site #	*Principal Investigator*	*location*	*# subjects contributed to Randomized dataset*	*# subjects contributed to Completers dataset*
1	Dr. Addison Taylor	Baylor College; Houston, TX	16	?
2	Dr. William Polvino	IBRD Center for Clin Research; Neptune, NJ	12	?
3	Dr. Alexander Shepherd	Univ. Texas; San Antonio, TX	7	?

[source: sponsor's report pg 9-10, vol 29]

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Study chronology

The chronology of the execution of this study was as follows:

Table: 5

Chronology of the execution of Study 94-5

Executed event	*Date*
Original protocol	5/23/95
First protocol amendment	6/28/95
Second protocol amendment	7/13/95
Final subject's last followup	2/29/96
Blind broken	4/4/96

[source: sponsor's submission dated 8/6/96, and study protocol]

Enrollment criteria.

Adult essential hypertension patients of either sex were eligible for enrollment if they manifested untreated mean supine DBPs between 95 and 119 mmHg and were without evidence of hypertensive end-organ damage.

Excluded from enrollment were pregnant or lactating women as well as those subjects manifesting:

- age less than 19 years.
- exposure to antihypertensive medications in the prior ten days, immunosuppressive agents within the year, phenothiazine or dopamine antagonists within 12 hours, illegal drugs at any time, ethanol (rate of use not specified) at any time, or any investigational drug within 30 days.
- secondary hypertension, or history of uncontrolled malignant ventricular arrhythmias.
- serum creatinine > 3 mg/dL, or requirement for any dialysis.
- SGOT or SGPT levels three times the upper limit of the normal.
- acute stroke, history of glaucoma or intraocular hypertension.
- history or findings of other cardiopulmonary, hepatic, hematologic, neurological, or unstable endocrinologic (such insulin-dependent diabetes mellitus, thyroid or adrenal) diseases.
- known hypersensitivity to catecholamines or sodium metabisulfite.

Qualifying criteria.

Pre-study Washout: During the outpatient medication washout phase of the study (prior to day 1) consenting subjects had any pre-existing antihypertensive agents discontinued for at least 10 days. At the end of this washout subjects were to have then qualified to enter the placebo run-in phase if they manifested a supine DBP ≥95 mmHg and ≤119 mmHg (on each of two consecutive visits spaced 3-10 days apart, with no greater than 7 mmHg variation between visits).

Placebo run-in (day 1): Subjects who were as-yet qualified after washout were then hospitalized,

given a 150 mEq/d sodium diet,[7] and entered into a 24 hour, single-blind, pre-randomization, placebo run-in phase during which previous antihypertensive medications continued to be withheld. During this run-in (study day 1) subjects were to receive (starting at 8 am) a placebo solution containing only the vehicle for the active drug preparation, infused at 0.5 mL/min through an indwelling antecubital venous catheter. Patients were to remain supine and fasting during the first 4 hours of the run-in. After that time they could eat and ambulate, but returned to bed every 15 minutes for BP recording (to be obtained after maintenance of supine posture for 5 minutes).

Subjects qualified for randomization if, during the first hour after the end of the placebo run-in, they manifested a mean (average of 3 observations) supine DBP ≥90 mmHg[8] and ≤119 mmHg.

Treatment regimen.

Randomized treatment (days 2-3): Starting at 9 am on day 2 (i.e. 25 rather than 24 hours after the start of the placebo run-in)[9] subjects who qualified for randomization were to receive a continuous, 48 hour, constant-rate, double-blind iv infusion of placebo or fenoldopam.

Each fenoldapam-randomized subject was intended to receive one of four fixed doses: X, 2.5X, 10X, and 20X (where X=0.04 μg/kg/min), i.e. 0.04, 0.1, 0.4, or 0.8 μg/kg/min[10].

Withdrawal (day 4): Immediately after discontinuation of the randomized infusion, a 24 hour study drug withdrawal phase ensued during which only vehicle was administered (as a placebo, during day 4).

Drug preparation and administration methods:

Fenoldopam was supplied at fixed concentration (10 mg/mL) in a single lot (U-93078) of 10 mL single-dose glass vials containing 10 mg/mL fenoldopam free-base. The contents of vials were diluted in vehicle (5% dextrose in water) in order to arrive at the final concentrations necessary for delivery, at fixed infusion rate, of the various intended doses. As noted above, the research pharmacist was unblinded in order to provide correct final concentrations.

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[7]this diet was to continue throughout the study.

[8]although this lower cutoff differs from the prespecified 95 mmHg threshold, there is no evidence that this change introduced any bias, e.g. there was no retrospective exclusion of any drug nonresponsive subject with SDBP between 90 and 95 mm.

[9]Note that this hour offset complicates the use of placebo run-in data as a control for circadian periodicity of outcome measures.

[10]as a result of a pharmacy error one subject who was randomized to 0.1 μg/kg/min actually received only one-tenth of the intended dose (0.01 μg/kg/min).

All infusions were intended to be at a rate of 0.5 mL/min, using calibrated pumps of the following types:

Table: 6

Infusion pumps used in Study 94-5:

site	*pump make/model*	*putatively lowest infusion rate achievable*	*FDA 510K number*
1	IMED Gemini PC-1	0.5 mL/min	883993
2	IMED PC1 IMED PC2	0.5 mL/min	--
3	AVI model 840	0.5 mL/min	--

[source: sponsor's submission dated 8/6/96]

Endpoints.

Descriptions

The primary PD endpoints were prespecified as systolic and diastolic arterial BP (postural position not specified), and heartrate (HR). Secondarily, hepatic blood flow estimates were also obtained.

The primary PK parameters were prespecified as time to steady state concentration, volume of distribution, blood to plasma concentration ratio, protein blinding percent, plasma concentration half-life (α and ß), plasma clearance, blood clearance, and plasma and urine metabolites.

The safety endpoints were as follows: observed adverse events (AE), hematology, blood chemistry, urinalysis, 12-lead electrocardiogram (EKG), and findings on physical examination.

Measurement methods

At the following times plasma drug sampling was undertaken (for determination of levels of racemic fenoldopam, R-fenoldopam, S-fenoldopam, and metabolites (methoxy-fenoldopam, sulfoxyfenoldopam and glucuronide conjugates):

> During randomized study drug infusion: at 0 min (i.e. the start of randomized treatment), 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, and 360 min, and every 6 hours thereafter (12, 18, 24, 30, 36, 42 and 48 hours).
>
> During study drug withdrawal: at 0 min (i.e. immediately at end of randomized study drug infusion), 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, 360 minutes, and then every 6 hours thereafter (12, 18 and 24 hours)

Urine Drug Samples: cumulative 12-hour urine samples were to be obtained (for assays of fenoldopam and metabolites) every 12 hours throughout the study.

BP and HR were generally monitored every 15 min throughout the study, with the exception of a higher sampling frequency (every 5 min) during the 2nd hour of randomized study drug infusion as well as during the first hour of the study drug withdrawal. Hemodynamic observations were to be

undertaken throughout the 24 hours following study drug withdrawal.

BPs were measured by a calibrated automated device (DINAMAP™ PLUS Vital Signs Monitor, Critikon, Inc; Model 8710 or 9710). These data were transfered electronically to Excel® software, and were also recorded in written source documents.

Hepatic blood flow estimates[11]: indocyanine green was administered at the end of the run-in, at the end of randomized study drug infusion, and at the end of study drug withdrawal. Blood samples (for hepatic blood flow determinations) were to be obtained immediately before and at 1, 3, 5, 7, 10, 13, 15, 17 and 20 minutes after each indocyanine green administration.

Sampling for laboratory test determinations was to be undertaken prior to randomized study drug infusion, during each day of randomized infusion[12], and at the end of study drug withdrawal.

EKG monitoring (12 lead) was to be undertaken at an unspecified time during the placebo run-in, every 6 hours during randomized study drug infusion, at the end of randomized study drug infusion, and any time a serious adverse event (AE) was observed.

Physical exams were performed prior to randomized study drug infusion, and at the end of study drug withdrawal.

Statistical analysis.

Prespecified Analyses

The primary prespecified analyses were a linear regression analysis of dose response (which is reviewed here), and a model-based estimation (non-linear, fixed effects) of PK parameters (see the Biopharmaceutics review for evaluation of this). A secondary analysis specified in the protocol was a random effects model-based[13] PK/PD analysis using NONMEM (see the Biopharmaceutics review for evaluation of this). All significance testing was to be performed at the type 1 error level of 5%.

No further detail about analytic approach was prespecified.

Sponsor's Posthoc definitions of "baseline"

After unblinding of the project statistician, various ways of defining baseline were retrospectively adopted [as per submission dated 11/1296]. The term "baseline" is defined differently in the different analyses submitted by the sponsor, and thus has no uniform, context-independent meaning in their report.

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[11]presumably this was of interest because the drug's blood clearance was felt to approximate hepatic blood flow.

[12]as per the protocol amendment dated 6/28/95.

[13]both linear and non-linear models were to be tested.

Baseline using Discrete-Time-since-infusion onset: here timepoint-by-timepoint comparisons were made of observations obtained at like timepoints since initiation of randomized vs placebo run-in infusions. These analyses did not strictly control for the circadian periodicity of hemodynamic measures because infusions were not synchronized to the same clocktime (i.e. the placebo run-in began at 8 am, whereas the randomized infusion was offset by one hour, beginning at 9 am).

Baseline using Hourly Average run-in measurement: Here baseline was defined as the mean of all observations obtained within a given hour after initiation of the placebo run-in infusion. With this method the sponsor employed temporal smoothing in the form of "rolled-up averages": for example, the observation ascribed to 2 hours post-infusion actually represented the mean of all mean values observed at the multiple observation points made throughout the hour leading up to hour 2 post-infusion (rather than the instantaneous observations made at hour 2).

Baseline using Whole-day Average run-in measurement: in other of the sponsor's analyses baseline was defined as the mean of all observations obtained during the 24 hours of placebo run-in (i.e. the daily average from day 1).

Other posthoc aspects of sponsor's analyses

Below are descriptions of additional posthoc aspects[14] of the linear regression analyses of dose response (only a general analytic approach, lacking in details, was specified in the protocol), as well as a characterization of the wholly retrospective pairwise t-test analyses.

The submitted linear regression analyses of dose-hemodynamic response were conducted by the sponsor in several different ways:

i) one regression analysis selected (from among the many available timepoints) only those observations obtained 0, 0.5, 1, 2, 3, 4, 6, 12, 18, 24, 36, and 48 hours after initiation of infusions; this used the daily average from the placebo run-in as baseline.

ii) another regression analyses was restricted solely to observations obtained 48 hr after initiation of study drug.

iii) another regression analysis was based on comparison of the mean of all measurements collected on given days.

The wholly posthoc pairwise t-test analyses evaluated changes (from the mean daily hemodynamic observations during the run-in) in fenoldopam-randomized and the parallel placebo group as observed at arbitrarily selected post-randomization timepoints (i.e. excluding all but the 4, 24, and 48 hours points post-randomization). These employed the "noncircadian" type definition of baseline, and did not temporally smooth observations.[15]

The submitted subgroup analysis of BP by gender was also not prespecified.

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[14]i.e. additional to the essentially posthoc definitions of "baseline".

[15]other than the process, described below, in which mistimed measurements were mapped to the nearest scheduled 15 minute timepoint.

Datasets prespecified.

There were no datasets prespecified for the sponsor's analysis. See the results section below for description of the datasets upon which the submitted analyses were ultimately based.

Sample size determination

There was no formal power calculation for this study.

Interim looks.

The sponsor reports that there was no interim look at data by anyone at Neurex Corporation, but that plasma drug level data were unblindly analyzed at Baylor University while the sponsor's Contract Research Organization reportedly kept Neurex personnel blinded.

Handling of missing data

There was no prespecification of the manner in which missing data would be handled. Missing data were excluded in the submitted analyses.

Handling of mistimed data collections

There was no prespecification of the manner in which mistimed data collections would be handled.

Multiplicity corrections

The sponsor retrospectively suggests that the pairwise t-tests comparing changes from run-in hemodynamics between different doseage groups be adjusted for multiplicity using Bonferroni's correction, setting α=0.05/5.

RESULTS (study 94-5).

Subject disposition.

The pertinent aspects of subject disposition were as follows:

- 38 subjects were enrolled.

  - 3/38 enrollees were not randomized after having insufficiently high BPs.

- 35 subjects were randomized.

  - 2/35 (i.e. subjects 2002 and 2009) were noted (post-randomization) to have failed to meet enrollment criteria (one had DBP of 82 mmHg while the other had no signed consent form). Neither received any randomized study drug, although they received placebo during the run-in. These subjects were excluded from the "dose received" analyses.

- 33 subjects were randomized and without violation of enrollment criteria.

- 4 were misdosed (receiving other than the randomized study drug or dose of study drug), but were included in the sponsor's dose-received or dose-randomized analyses.

- 3/4 of these misdosings were sponsor-attributed to misrandomization. These misdosings were as follows:
  - 1 was placebo-randomized but received 0.8 µg/kg/min drug.
  - 1 was randomized to 0.4 µg/kg/min, but received placebo.
  - 1 was randomized to 0.4 µg/kg/min, but received 0.04.

- 1/4 of these misdosings, attributed to pharmacy error, involved randomization to 0.1 µg/kg/min, but administration of 0.01 µg/kg/min.

- 1 randomized subject (#2007) dropped out (after 31 hours of randomized infusion) because of forearm hematomas resulting in inadequate iv access (see below discussion of safety data), but was included in both the "dose received" and "dose randomized" analyses.

- 32 subjects were completers who received either the randomized or an erroneous dose (i.e. that attributed to pharmacy error).

- 3 fenoldopam-randomized completers were previously exposed to fenoldopam, and shown to be responsive to its antihypertensive effect in the pilot study reviewed below.

- 31 subjects were completers who received the randomized dose.

Datasets on which submitted analyses were based

In the absence of prespecification of datasets, the submitted analyses were based on the following datasets:

- Per dose randomized: in this dataset the dose attributed to a subject was the randomized dose.
- Per dose received: in this dataset the dose attributed to a subject was the actual dose received.

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Pre-treatment covariates in the analyzed datasets.

Demographic and pre-treatment characteristics of subjects are shown in the following two tables. In each dataset there was some degree of imbalance with respect to the distribution of race and sex.

Table: 7

Demographic and Pre-treatment characteristics of subjects in study 94-5: Dose-Randomized dataset

	Concurrent Placebo	*Fenoldopam (µg/kg/min)*			
		0.04	*0.1*	*0.4*	*0.8*
sample size	7	7	9	7	7
Age mean (yr)	49	56	48	45	56
Black (%)	43	14	11	43	60
Caucasian (%)	43	86	78	57	20
Male (%)	43	86	89	86	100
Female (%)	57	14	11	14	0
Mean DBP at end of run-in (mm Hg)	100.1	98.5	100.6	99.3	100.8

[source: modification of table 2-17, addendum dated 11/12/96]

Table: 8

Demographic and Pre-treatment characteristics of subjects in study 94-5: Dose-Received Dataset

	Concurrent Placebo	*Fenoldopam (µg/kg/min)*			
		0.04	*0.1*	*0.4*	*0.8*
sample size	7	7	7	5	6
Age mean (yr)	49	55	49	47	54
Black (%)	29	29	0	40	67
Caucasian (%)	57	71	86	60	17
Male (%)	43	86	100	80	100
Female (%)	57	14	0	20	0
Mean DBP at end of run-in (mm Hg)	101.3	98.6	102	98.8	99.7

[source: modification of table 2-17, addendum dated 11/12/96]

The above summary of central tendencies does not include the single subject receiving a 0.01 µg/kg/min dose.

Drug exposures: Deviation between Prespecified and Actual:

The range of actual clocktimes at the start of the placebo run-in infusion was 7:45 am to 9:25 am. The range of actual clocktimes at the start of randomized drug was 9:02 am to 10:46 am.

With respect to nonrandomized pharmacologic agents, one subject was co-exposed to unstable doses of an agent which could have plausibly influenced hemodynamic outcomes, i.e. 30 mg of pseudoephedrine was administered on study day 2 only (subject 1006).

Timing of endpoint observations: Deviation between Prespecified and Actual:

A relatively small fraction (1.5%) of hemodynamic observations were collected at an interval of more than 7.5 minutes before or after the intended time (the fraction of mistimed plasma concentration observations was not described by the sponsor); nearly half of these were during the placebo run-in.

Posthoc (and after unblinding), those mistimed measurements collected ± 7.5 minutes from the specified time were mapped to the nearest scheduled 15 minute timepoint. If more than one measurement were available within these intervals, all but the one nearest the 15 minute margin was excluded (197 observations were excluded from the analyses on this basis).

Response in demographic subgroups

Given the small sample of 6 females, there is little conclusive inference to be drawn from a posthoc subgroup analysis of BP results by gender.

SAFETY OUTCOMES •

Deaths and Dropouts:

There were reportedly no deaths in study 94-5. One randomized subject dropped out (after 31 hours of randomized infusion) because of bilateral forearm hematomas which limited iv access. There was reportedly no evidence in this subject of any drug-associated basis for bleeding, such as thrombocytopenia or liver function abnormality.

Common AE:

Among 33 fenoldopam-treated subjects the most frequently reported AEs among subjects were headache (37%), ST-T wave abnormality (6% vs none in the placebo group), "other EKG abnormalities" [not defined, except for being other than ST-T wave changes] (9%), and "dizziness" [undefined] (9%).

A single subject experienced orthostatic hypotension not requiring discontinuation from the study. Headache did not demonstrate a monotonic relationship to dose over the entire dose range, but "dizziness" showed a weak signal of dose-relatedness.

One subject with past history of MI experienced typical angina 5 days after the study's end.

EKG findings:

In four subjects (one of which had pre-existing left ventricular hypertrophy) treatment-emergent,

persistent ST depression and/or T wave inversion abnormalities were reported [as per submission dated 1/13/97]. Some, but not all of these findings persisted throughout the observation period. There was some suggestion, although not definitive, that these effects had a monotonic relationship to dose.
Lesser findings (classified as "other EKG abnormalities") were reported as clinically insignificant and without requirement for discontinuation of drug.

Laboratory findings:

No sampling for laboratory measurements (blood chemistry or hematology tests) was undertaken during randomized therapy. The submitted data describe changes from the placebo run-in to the end of the study (the final measurement by and large represented the observations obtained a full day subsequent to drug withdrawal).

Given the short half-life of fenoldopam, this was plausibly an insensitive method of assay for transient, concentration-related adverse laboratory phenomenon. Not surpisingly, it reportedly demonstrated little in the way of significant changes. A mean 55% decrease from pretreatment level of platelet count was observe, however, at the end of study in the 0.8 µg/kg/min dose group. The duration of this finding was not described, but it reportedly was without clinical sequelae.

2.2 Pilot PK/PD study in essential hypertensives (study 94-7)

Design Summary

This open-label, baseline placebo-controlled, parallel-group, dose-ranging PK/PD pilot study randomized 8 subjects (moderate to severe essential hypertension patients without evidence of end-organ damage) to receive a 48 hour iv infusion of fenoldopam (given as a fixed 0.4, 0.6, 0.8, or 1.6 µg/kg/min dose). Prior to randomization there was a 24 hour placebo lead-in (Day 1), and the lead-in was preceded by a 21 day washout of previous antihypertensive medications. After 2 days of randomized study drug infusion there was a 24 hour study drug withdrawal phase (on Day 4) during which placebo was administered. The principal measured parameters were systemic arterial BP, HR, and plasma concentration of parent drug and metabolites. The objectives were to preliminarily assess for maximally effective dose, characterize PK parameters, and to observe for any evidence of tolerance.

The temporal sequence of phases in this study was as follows:

Table: 9

Temporal sequence of the phases of study 94-7

Days "minus 21 to 0"	*Day "1"*	*Days "2->3"*	*Day "4"*
pre-study medication washout	placebo run-in	randomized study drug infusion	study drug withdrawal (placebo given)

Investigative site

The principal investigator of this single-center study was Dr. James Pool of Methodist Hospital,

Houston, Texas.

Study chronology.

The chronology of the execution of this study was as follows:

Table: 10

Chronology of the execution of Study 94-7

Executed event	*Date*
Original protocol submission date	1/19/95
First protocol amendment	2/9/95
Second protocol amendment	2/9/95
Third protocol amendment	3/10/95
Fourth protocol amendment	3/10/95
Last subject's final followup	5/11/95

[source: submission dated 8/6/96]

Enrollment criteria.

Adult essential hypertension patients of either sex were eligible for enrollment if they manifested untreated mean supine DBPs between 105 and 119 mmHg and were without evidence of hypertensive end-organ damage.

The exclusion criteria were essentially those of study 94-5. Excluded from enrollment were pregnant or lactating women as well as those subjects manifesting:

- age less than 19 years.
- exposure to antihypertensive medications in the prior ten days, immunosuppressive agents within the year, phenothiazine or dopamine antagonists within 12 hours, illegal drugs at any time, ethanol (rate of use not specified) at any time, or any investigational drug within 30 days.
- secondary hypertension, or history of uncontrolled malignant ventricular arrhythmias.
- serum creatinine > 2 mg/dL, or requirement for any dialysis.
- SGOT or SGPT levels three times the upper limit of the normal.
- acute stroke, history of glaucoma or intraocular hypertension.
- history or findings of other cardiorenal, pulmonary, hepatic, hematologic, neurological, or unstable endocrinologic diseases.
- known hypersensitivity to catecholamines or sodium metabisulfite

Qualifying criteria.

Pre-study Washout: During the outpatient medication washout phase of the study (prior to day 1) consenting subjects had any pre-existing antihypertensive agents discontinued for at least 21 days [note this is one of the differences rel to study 94-5]. At the end of this washout subjects were to have then qualified to enter the placebo run-in phase if, they manifested a supine DBP ≥105 mmHg

and ≤119 mmHg (on each of two consecutive visits spaced 3-10 days apart, with no greater than 7 mmHg variation between visits).

Placebo run-in (day 1): Subjects as-yet qualified after washout were hospitalized, given a 150 mEq/d sodium diet, and entered into a 24 hour, open-label, pre-randomization, placebo run-in phase during which previous antihypertensive medications continued to be withheld. During this run-in (study day 1) subjects were to receive (starting at 8 am) a placebo solution containing only the vehicle for the active drug preparation, infused at 1 mL/min through an indwelling antecubital venous catheter. Patients were to remain supine and fasting during the first 4 hours of the run-in. After that time they could eat and ambulate, but returned to bed every 15 minutes for BP recordings (to be obtained after maintenance of supine posture for 5 minutes).

Subjects were qualified to be randomized if, at end of the placebo run-in, they manifested a mean (average of 4 observations) supine DBP ≥95 mmHg and <120 mmHg.

Treatment regimen.

Randomized treatment (days 2-3): Subjects qualified for randomization were to receive (starting at 9 am on day 2) a continuous, 48 hour, constant-rate, open-label iv infusion of fenoldopam. The first 4 qualified subjects were assigned to one of the two prespecified high-dose arms (0.8 or 1.6 µg/kg/min). After half of these subjects temporarily experienced undesirably large BP reductions (further discussion is found below) the protocol was revised by adding medium-dose arms (0.4 and 0.6 µg/kg/min), eliminating the originally planned low-dose arms (concurrent placebo and 0.1 µg/kg/min), but keeping the high-dose arms.

The final four qualified subjects were to be randomized to one of four dose levels: X, 1.5X, 2X, and 4X (where X= 0.4 µg/kg/min), i.e. 0.4, 0.6, 0.8, or 1.6 µg/kg/min.

Withdrawal (day 4): Immediately after discontinuation of the randomized infusion, a 24 hour study drug withdrawal phase ensued during which only vehicle was administered (as a placebo, during day 4).

Drug preparation and administration methods

Fenoldopam was supplied at fixed concentration (10 mg/mL) in a single lot (U-93078) of 10 mL single-dose glass vials containing 100 mg/vial. The contents of all vials were diluted in vehicle (5% dextrose in water) to the same final concentration (100 µg/mL) for each dose arm. All infusions used an IMED pump with the following characteristics:

Table: 11

Infusion pumps used in Study 94-7:

site	*pump make/model*	*putative lowest infusion rate achievable*	*FDA 510K number*
001	IMED Gemini PC-1	0.5 mL/min	883993

[source: modification of table submitted 8/6/96]

During the run-in, placebo (vehicle solution) was infused at an intended rate of 1 mL/min. The

fenoldopam infusion flow rates required to achieve the intended fixed dosing rates of 0.4, 0.6, 0.8, or 1.6 μg/kg/min were 0.004, 0.006, 0.008, and 0.016 mL/kg/min, respectively.

Endpoints.

Descriptions

The details of endpoint selection were not prespecified. The reported safety endpoints were as follows: observed adverse events (AE), hematology, blood chemistry, urinalysis, 12-lead electrocardiogram (EKG), and findings on physical examination (done on days 1 and 4).

Measurement methods

At the following times plasma drug sampling was undertaken (with the same intended frequency as in study 94-5) for determination of levels of racemic fenoldopam and metabolites.

During randomized study drug infusion: at 0 min (the intended clocktime was 9 am), 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, and 360 min, and every 6 hours thereafter (12, 18, 24, 30, 36, 42 and 48 hours).

During study drug withdrawal: at 0 min (i.e. immediately at end of randomized study drug infusion), 5, 10, 20, 30, 45, 60, 120, 180, 240, 300, 360 minutes, and then every 6 hours thereafter (12, 18 and 24 hours).

Urine Drug Samples: cumulative 12-hour urine samples were to be obtained (for assays of fenoldopam and metabolites) every 12 hours throughout the study.

BP and HR were monitored with the same intended frequency as in study 94-5. Sampling for these parameters was generally every 15 min throughout the study, with the exception of a higher sampling frequency (every 5 min) during the first hour of randomized study drug infusion as well as during the first hour of the study drug withdrawal. Hemodynamic observations were to be undertaken throughout the 24 hours following study drug withdrawal.

BPs were measured by a calibrated, automated, oscillometric device (DINAMAP™ PLUS Vital Signs Monitor; Critidon, Inc, Model 8710).

Hepatic blood flow estimates: indocyanine green was administered at the end of the run-in, at the end of randomized study drug infusion, and at the end of study drug withdrawal. Blood samples (for hepatic blood flow determinations) were to be obtained immediately before and at 1, 3, 5, 7, 10, 13, 15, 17 and 20 minutes after each indocyanine green administration [but these data were not reported].

Sampling for laboratory test determinations was to be undertaken at unspecified times prior to randomized study drug infusion, during randomized infusion day 1, and at the end of study.

EKG monitoring (12 lead) was undertaken prior to study drug infusion, and at the end of study drug infusion.

Physical exams were performed prior to randomized study drug infusion, and at the end of study drug withdrawal.

STATISTICAL ANALYSES.

Prespecified Analyses

No statistical analyses were planned.

Posthoc analyses or aspects of analyses

Posthoc descriptive analyses presented drug-associated hemodynamic changes from run-in, on a timepoint-by-timepoint basis.

The sponsor assessed tolerance to the effects of fenoldopam effects by comparing hemodynamic measurements during the 2nd day of study drug to those obtained during the 1st day of drug exposure.

The sponsor assessed the offset of fenoldopam effects by comparing hemodynamic measurements post-withdrawal to those obtained during the 2nd day of study drug.

Rebound was retrospectively defined as a sustained (≥30 minute) post-withdrawal increase in SBP or DBP of at least 35 mm Hg above the run-in value at like clocktimes.

Sample size determination

There was no formal power calculation which underlied the sizing of this study.

Interim Look

The data from the first 4 patients were assessed on an interim basis.

Handling of missing data

There was no prespecification of the manner in which missing data would be handled. Missing data were generally excluded in the submitted analyses.

Handling of mistimed data collections

There was no prespecification of the manner in which mistimed observations would be handled. A procedure for handling the mistimed observations was initiated by the sponsor as follows: mistimed measurements which were closest to each scheduled timepoint were selected after grouping available measurements into 5 or 15 minute intervals around scheduled timepoints. If more than one measurement were available within these intervals, all but one would be excluded according to unspecified criteria.