CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76656

Name: Fenoldopam Mesylate, 10 mg (base)/mL

Sponsor: Luitpold Pharmaceuticals, Inc.
(formerly PharmaForce, Inc.)

Approval Date: December 1, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

APPROVAL LETTER

ANDA 76-656

DEC 1 2003

PharmaForce, Inc.
Attention: Marilyn A. Friedly
1507 Chambers Road
Columbus, OH 43212

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 31, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fenoldopam Mesylate Injection USP, 10 mg (base)/mL, packaged in 10 mg (base)/1 mL and 20 mg (base)/2 mL single-dose ampoules.

Reference is also made to your amendments dated August 1, August 4, and September 23, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Fenoldopam Mesylate Injection USP, 10 mg (base)/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Corlopam® Injection USP, 10 mg (base)/mL, of Abbott Laboratories - Hospital Products Division).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 12/1/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-656
Division File
Field Copy
HFD-610/R. West
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HFD-205
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Endorsements:
HFD-623/R.D'Costa/
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HFD-617/C.Kiester/
HFD-613/J.Barlow/
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HFD-600/N.Nath/
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APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

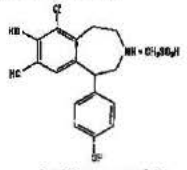
LABELING

FENOLDOPAM MESYLATE INJECTION, USP

Rx Only

DESCRIPTION

Fenoldopam mesylate injection, USP is a dopamine D_1-like receptor agonist. The product is formulated as a solution to be diluted for intravenous infusion. Chemically it is 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-[1*H*]-3-benzazepine-7,9-diol methanesulfonate with the following structure:



fenoldopam mesylate

Fenoldopam mesylate is a white to off-white powder with a molecular weight of 401.87 and a molecular formula of $C_{16}H_{16}ClNO_3{\cdot}CH_4SO_3H$. It is sparingly soluble in water, ethanol and methanol, and is soluble in propylene glycol.

Ampoules: Each 1 mL contains fenoldopam mesylate equivalent to fenoldopam 10 mg; propylene glycol 518 mg; citric acid 3.44 mg; sodium citrate dihydrate 0.81 mg; sodium metabisulfite 1 mg; water for injection; pH range of 2.8 to 3.8.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fenoldopam is a rapid-acting vasodilator. It is an agonist for D_1-like dopamine receptors and binds with moderate affinity to α_2-adrenoceptors. It has no significant affinity for D_2-like receptors, α_1 and β adrenoceptors, $5HT_1$ and $5HT_2$ receptors, or muscarinic receptors. Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. The R-isomer has approximately 250-fold higher affinity for D_1-like receptors than does the S-isomer. In non-clinical studies, fenoldopam had no agonist effect on presynaptic D_2-like dopamine receptors, or α- or β-adrenoceptors, nor did it affect angiotensin-converting enzyme activity. Fenoldopam may increase norepinephrine plasma concentration.

In animals, fenoldopam has vasodilating effects in coronary, renal, mesenteric and peripheral arteries. All vascular beds, however, do not respond uniformly to fenoldopam. Vasodilating effects have been demonstrated in renal efferent and afferent arterioles. In humans, increases in renal blood flow were demonstrated in hypertensive and normal subjects treated with intravenous fenoldopam in two small controlled trials. No beneficial clinical effect on renal function has been shown in patients with heart failure or hepatic or severe renal disease.

Pharmacokinetics

Administered as a constant infusion at rates of 0.01 to 1.6 µg/kg/min, fenoldopam produced steady-state plasma concentrations that were proportional to infusion rates. The elimination half-life was about 5 minutes in mild to moderate hypertensives, with little difference between the R (active) and S isomers. Steady state concentrations are attained in about 20 minutes (4 half-lives). The steady state plasma concentrations of fenoldopam, at comparable infusion rates, were similar in normotensive subjects and in patients with mild to moderate hypertension or hypertensive emergencies (Table 1).

Table 1
Fenoldopam Plasma Concentrations in Normotensive, Mild to Moderate and Malignant Hypertensive Patients
FENOLDOPAM PLASMA CONCENTRATION (ng/mL)

	Patient Populations		
Fenoldopam Infusion Rate (µg/kg/min)	Normotensive Subjects n=10	Mild to Moderate Hypertensive Patients n=7	Malignant Hypertension Patients n=20
0.1	3.2	4.0	3.3

Clearance of parent (active) fenoldopam is not altered in patients with end-stage renal disease on continuous ambulatory peritoneal dialysis (CAPD) and is not affected on average, in severe hepatic failure. The effects of hemodialysis on the pharmacokinetics of fenoldopam have not been evaluated.

In radiolabeled studies in rats, no more than 0.006% of fenoldopam crossed the blood-brain barrier.

Excretion and Metabolism

Radiolabeled studies show that about 90% of infused fenoldopam is eliminated in urine, 10% in feces. Elimination is largely by conjugation, without participation of cytochrome P-450 enzymes. The principal routes of conjugation are methylation, glucuronidation, and sulfation. Only 4% of the administered dose is excreted unchanged. Animal data indicate that the metabolites are inactive.

Special Populations: The pharmacokinetics of fenoldopam were not influenced by age, gender, or race in hypertensive emergency patients. Effects of renal and hepatic dysfunction are described above. There have been no formal drug-drug interaction studies using intravenous fenoldopam.

Pharmacodynamics and Clinical Studies

In a randomized double-blind, placebo-controlled, 5-group study in 32 patients with mild to moderate essential hypertension (diastolic blood pressure between 95 and 119 mm Hg), and a mean baseline pressure of about 164/98 mm Hg, and heart rate of about 75 bpm, fixed-rate IV infusions of fenoldopam produced dose-related reductions in systolic and diastolic blood pressure. Infusions were maintained at a fixed rate for 48 hours. Table 2 shows the results of the study. The onset of response was rapid at all infusion rates, with the 15-minute response representing 50 to 100% of the one-hour response in all groups. There was some suggestion of partial tolerance at 48 hours in the two higher dose infusions, but a substantial effect persisted through 48 hours. When infusions were stopped, blood pressure gradually returned to pretreatment values with no evidence of rebound. This study suggests that there is no greater response to 0.8 µg/kg/min than to 0.4 µg/kg/min.

Table 2
PHARMACODYNAMIC EFFECTS OF FENOLDOPAM IN MILD TO MODERATE HYPERTENSIVE PATIENTS

	Infusion Rate (µg/kg/min)				
Time Point and Mean Change From Time Zero ± SE	Placebo n = 7	0.04 n = 7	0.1 n = 7	0.4 n = 5	0.8 n = 6
15 Minutes of Infusion*					
Systolic BP	0 ± 6	-15 ± 6	-19 ± 8	-14 ± 4	-24 ± 6
Diastolic BP	0 ± 2	-5 ± 3	-12 ± 4	-15 ± 3	-20 ± 4
Heart rate	+2 ± 2	+3 ± 2	+5 ± 1	+16 ± 3	+19 ± 3
30 Minutes of Infusion*					
Systolic BP	-8 ± 5	-17 ± 6	-18 ± 6	-14 ± 8	-26 ± 6
Diastolic BP	-6 ± 3	-7 ± 3	-16 ± 4	-14 ± 3	-20 ± 2
Heart rate	+2 ± 2	+3 ± 2	+10 ± 2	+16 ± 3	+23 ± 3
1 Hour of Infusion*					
Systolic BP	-15 ± 4	-22 ± 7	-22 ± 7	-26 ± 9	-22 ± 9
Diastolic BP	-5 ± 3	-9 ± 2	-18 ± 4	-19 ± 4	-21 ± 1
Heart rate	+1 ± 3	+5 ± 2	+12 ± 3	+19 ± 4	+25 ± 4
4 Hours of Infusion*					
Systolic BP	-14 ± 5	-16 ± 9	-31 ± 15	-22 ± 11	-25 ± 7
Diastolic BP	-14 ± 6	-8 ± 4	-19 ± 9	-25 ± 3	-20 ± 1
Heart rate	+5 ± 3	+6 ± 3	+10 ± 4	+21 ± 2	+27 ± 7
24 Hours of Infusion*					
Systolic BP	-20 ± 6	-23 ± 8	-35 ± 7	-22 ± 6	-23 ±11
Diastolic BP	-11 ± 6	-11 ± 5	-23 ± 10	-22 ± 5	-13 ± 3
Heart rate	+6 ± 3	+5 ± 3	+13 ± 2	+17 ± 4	+15 ± 3
48 Hours of Infusion*					
Systolic BP	-12± 8	-31± 5	-22 ± 8	-9 ± 6	-14 ± 10
Diastolic BP	-3 ± 5	-10 ± 6	-9 ± 7	-9 ± 2	-9 ± 3
Heart rate	+1 ± 2	0 ± 4	+1 ± 4	+12 ± 3	+8 ± 3

*Mean change from time zero ± S.E.

In a multicenter, randomized, double-blind comparison of four infusion rates, fenoldopam was administered as constant rate infusions of 0.01, 0.03, 0.1 and 0.3 µg/kg/min for up to 24 hours to 94 patients experiencing hypertensive emergencies (defined as diastolic blood pressure ≥ 120 mm Hg with evidence of compromise of end-organ function involving the cardiovascular, renal, cerebral or retinal systems). Infusion rates could be doubled after one hour if clinically indicated. There were dose-related, rapid-onset, decreases in systolic and diastolic blood pressures and increases in heart rate (Table 3).

Table 3
PHARMACODYNAMIC EFFECTS OF FENOLDOPAM IN HYPERTENSIVE EMERGENCY PATIENTS

	Infusion Rate µg/kg/min			
Time Point and Pharmacodynamic Parameters	0.01 n = 25	0.03 n = 24	0.1 n = 22	0.3 n = 23
Pre-Infusion Baseline				
Systolic BP - mean ± SE	210 ± 21	208 ± 26	205 ± 24	211 ± 17
Diastolic BP - mean ± SE	136 ± 16	135 ± 11	133 ± 14	136 ± 15
Heart rate - mean ± SE	87 ± 20	84 ± 14	81 ± 19	80 ± 14
15 Minutes of Infusion*				
Systolic BP	-5 ± 4	-7 ± 4	-16 ± 4	-19 ± 4
Diastolic BP	-5 ± 3	-8 ± 3	-12 ± 2	-21 ± 2
Heart rate	-2 ± 3	+1 ± 1	+2 ± 1	+11 ± 2
30 Minutes of Infusion*				
Systolic BP	-6 ± 4	-11 ± 4	-21 ± 3	-16 ± 4
Diastolic BP	-10 ± 3	-12 ± 3	-17 ± 3	-20 ± 2
Heart rate	-2 ± 3	-1 ± 1	+3 ± 2	+12 ± 3
1 Hour of Infusion*				
Systolic BP	-5 ± 3	-9 ± 4	-19 ± 4	-22 ± 4
Diastolic BP	-8 ± 3	-13 ± 3	-18 ± 2	-23 ± 2
Heart rate	-1 ± 3	0 ± 2	+3 ± 2	+11 ± 3
4 Hours of Infusion*				
Systolic BP	-14 ± 4	-20 ± 5	-23 ± 4	-37 ± 4
Diastolic BP	-12 ± 3	-18 ± 3	-21 ± 3	-29 ± 3
Heart rate	-2 ± 4	0 ± 2	+4 ± 2	+11 ± 2

*Mean change from baseline ± S.E.

Two hundred and thirty six severely hypertensive patients (DBP ≥ 120 mm Hg), with or without end-organ compromise, were randomized to receive in two open-label studies either fenoldopam or nitroprusside. The response rate was 79% (92/117) in the fenoldopam group and 77% (90/119) in the nitroprusside group. Response required a decline in supine diastolic blood pressure to less than 110 mm Hg if the baseline were between 120 and 150 mm Hg, inclusive, or by ≥ 40 mm Hg if the baseline were ≥ 150 mm Hg. Patients were titrated to the desired effect. For fenoldopam, the dose ranged from 0.1 to 1.5 µg/kg/min; for nitroprusside, the dose ranged from 1.0 to 8.0 µg/kg/min. As in the study in mild to moderate hypertensives, most of the effect seen at one hour is present at 15 minutes. The additional effect seen after 1 hour occurs in all groups and may not be drug-related (there was no placebo group to evaluate this).

INDICATIONS AND USAGE

Fenoldopam mesylate injection is indicated for the in-hospital, short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function. Transition to oral therapy with another agent can begin at any time after blood pressure is stable during fenoldopam infusion.

CONTRAINDICATIONS

None known.

WARNINGS

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

Intraocular Pressure: In a clinical study of 12 patients with open-angle glaucoma or ocular hypertension (mean baseline intraocular pressure was 29.2 mm Hg with a range of 22.0 to 33.0 mm Hg), infusion of fenoldopam at escalating doses ranging from 0.05 to 0.5 µg/kg/min over a 3.5 hour period caused a dose-dependent increase in intraocular pressure (IOP). At the peak effect, the intraocular pressure was raised by a mean of 6.5 mm Hg (range -2.0 to +8.5 mm Hg, corrected for placebo effect). Upon discontinuation of the fenoldopam infusion, the IOP returned to baseline values within 2 hours. Fenoldopam administration to patients with glaucoma or intraocular hypertension should be undertaken with caution.

Tachycardia: Fenoldopam causes a dose-related tachycardia (Table 2 and Table 3), particularly with infusion rates above 0.1 µg/kg/min. Tachycardia diminishes over time but remains substantial at higher doses.

Hypotension: Fenoldopam may occasionally produce symptomatic hypotension and close monitoring of blood pressure during administration is essential (See Adverse Reactions). It is particularly important to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.

Hypokalemia: Decreases in serum potassium occasionally to values below 3.0 meq/L were observed after less than 6 hours of fenoldopam infusion. It is not clear if the hypokalemia reflects a pressure natriuresis with enhanced potassium-sodium

exchange or a direct drug effect. During clinical trials, electrolytes were monitored at intervals of 6 hours. Hypokalemia was treated with either oral or intravenous potassium supplementation. Patient management should include appropriate attention to serum electrolytes.

Drug Interactions: Although there have been no formal interaction studies, intravenous fenoldopam has been administered safely with drugs such as digitalis and sublingual nitroglycerin. There is limited experience with concomitant antihypertensive agents such as beta-blockers, alpha-blockers, calcium channel-blockers, ACE inhibitors, and diuretics (both thiazide-like and loop).

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study, mice treated orally with fenoldopam at 12.5, 25, or 50 mg/kg/day, reduced to 25 mg/kg/day on day 268 of study, showed no increase above controls in the incidence of neoplasms. Female mice in the highest dose group had an increased incidence and degree of severity of a fibro-osseous lesion of the sternum compared with control or low-dose animals. Compared to controls, female mice in the middle- and upper-dose groups had a higher incidence and degree of severity of chronic nephritis. These pathologic lesions were not seen in male mice treated with fenoldopam.

In a 24-month study, rats treated orally with fenoldopam at 5, 10 or 20 mg/kg/day, with the mid- and high-dose groups increased to 15 or 25 mg/kg/day, respectively, on day 372 of the study, showed no increase above controls in the incidence or type of neoplasms. Compared with the controls, rats in the mid- and high-dose groups had a higher incidence of hyperplasia of collecting duct epithelium at the tip of the renal papilla.

In *in vitro* assays, fenoldopam did not induce bacterial gene mutation in the Ames test or mammalian gene mutation in the Chinese hamster ovary (CHO) cell assay. In the *in vitro* chromosomal aberration assay with CHO cells, fenoldopam was associated with statistically significant and dose-dependent increases in chromosomal aberrations, and in the proportion of aberrant metaphases. However, no chromosome damage was seen in the *in vivo* mice micronucleus or bone marrow assays. The data support the conclusion that fenoldopam is not genotoxic or clastogenic.

Oral fertility and general reproduction performance studies in male and female rats at 12.5, 37.5 or 75 mg/kg/day revealed no impairment of fertility or reproduction performance due to fenoldopam.

Pregnancy: *Pregnancy Category B.* Oral reproduction studies have been performed in rats and rabbits at doses of 12.5 to 200 mg/kg/day and 6.25 to 25 mg/kg/day, respectively. Studies have revealed maternal toxicity at the highest doses tested but no evidence of impaired fertility or harm to the fetus due to fenoldopam. However, there are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, fenoldopam should be used in pregnancy only if clearly needed.

Nursing Mothers: Fenoldopam is excreted in milk in rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fenoldopam is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Fenoldopam causes a dose-related fall in blood pressure and increase in heart rate (see Precautions, Tachycardia, and Hypotension). In controlled clinical studies of severe hypertension in patients with end-organ damage, 3% (4/137) of patients withdrew because of excessive falls in blood pressure. Increased heart rate could, in theory, lead to ischemic cardiac events or worsened heart failure, although these events have not been observed. The most common events reported as associated with fenoldopam use are headache, cutaneous dilation (flushing), nausea, and hypotension, each reported in more than 5% of patients.

Adverse reactions in controlled trials in hypertension

Adverse events occurring more than once in any dosing group (once if potentially important or plausibly drug-related) in the fixed-dose constant-infusion studies are presented in the following Table by infusion-rate group. There was no clear dose relationship, except possibly for headache, nausea, flushing.

Table 4

ADVERSE EVENTS* FROM FIXED-DOSE INFUSION STUDIES BY DOSE GROUP

		Fenoldopam Dose (µg/kg/min)					
Body System	**Event**	**Placebo (n = 7)**	**0.01 (n = 25)**	**0.03-0.04 (n = 31)**	**0.1 (n = 25)**	**0.3-0.4 (n = 23)**	**0.6-0.8 (n = 11)**
Body, General	Headache	1	5	4	7	8	6
	Injection site reaction	0	1	3	0	3	2
Cardiovascular	ST-T abnormalities (primarily T-wave inversion)	0	2	4	0	1	0
	Flushing	0	0	0	0	1	3
	Hypotension**	0	0	0	2	0	2
	Postural hypotension	0	2	0	0	0	0
	Tachycardia**	0	0	0	0	0	2
Digestive	Nausea	0	3	0	3	5	4
	Vomiting	0	2	0	2	1	2
	Abdominal pain/ fullness	0	2	0	0	2	1
	Constipation	0	0	0	0	0	3
	Diarrhea	0	0	0	0	2	0
Metabolic and Nutritional	Increased creatinine**	0	0	2	0	0	0
	Hypokalemia**	0	2	2	0	1	0
Nervous	Nervousness/ anxiety	0	0	1	0	0	2
	Insomnia	0	2	0	0	0	0
	Dizziness	0	1	1	2	2	0
Respiratory	Nasal congestion	0	0	0	0	0	2
Skin and Appendages	Sweating	0	0	0	1	1	2
Urogenital	Urinary tract infection	0	2	0	1	0	0
Musculoskeletal	Back pain	0	1	0	1	2	2

* Includes events reported by 2 or more patients receiving fenoldopam treatment across all dose groups.

** Investigator defined; no protocol definition

Adverse effects in overall data base

The adverse event incidences listed below are based on observations of over 1,000 fenoldopam treated patients and not listed in the Table above.

Events reported with a frequency between 0.5 to 5% in patients treated with IV fenoldopam:

Cardiovascular: extrasystoles, palpitations, bradycardia, heart failure, ischemic heart disease, myocardial infarction, angina pectoris

Metabolic: elevated BUN, elevated serum glucose, elevated transaminase, elevated LDH

General Body: non-specific chest pain, pyrexia

Hematological/Lymphatic: leukocytosis, bleeding

Respiratory: dyspnea, upper respiratory disorder

Genitourinary: oliguria

Musculoskeletal: limb cramp

ANIMAL TOXICOLOGY

Unusual toxicologic findings (arterial lesions in the rat) with fenoldopam are summarized below. These findings have not been observed in mice or dogs. No evidence of a similar lesion in humans has been observed.

Arterial lesions characterized by medial necrosis and hemorrhage have been seen in renal and splanchnic arteries of rats given fenoldopam mesylate by continuous intravenous infusion at doses of 1 to 100 µg/kg/min for 24 hours. The incidence of these lesions is dose related. Arterial lesions morphologically identical to those observed with fenoldopam have been reported in rats infused with dopamine. Data suggest that the mechanism for this injury involves activation of D$_1$-like dopaminergic receptors. Such lesions have not been seen in dogs given doses up to 100 µg/kg/min by continuous intravenous infusion for 24 hours, nor were they seen in dogs infused at the same dose for 8 hours daily for 24 days. The clinical significance of this finding is not known.

Oral administration of fenoldopam doses of 10 to 15 mg/kg/day or 20 to 25 mg/kg/day to rats for 24 months induced a higher incidence of polyarteritis nodosa compared to controls. Such lesions were not seen in rats given 5 mg/kg/day of fenoldopam or in mice given the drug at doses up to 50 mg/kg/day for 24 months.

OVERDOSAGE

Intentional fenoldopam overdosage has not been reported. The most likely reaction would be excessive hypotension which should be treated with drug discontinuation and appropriate supportive measures.

DOSAGE AND ADMINISTRATION

The optimal magnitude and rate of blood pressure reduction in acutely hypertensive patients have not been rigorously determined, but, in general, both delay and too rapid decreases appear undesirable in sick patients. An initial fenoldopam mesylate injection dose may be chosen from Tables 2 and 3 in the Clinical Pharmacology Section that produces the desired magnitude and rate of blood pressure reduction in a given clinical situation. Doses below 0.1 µg/kg/min have very modest effects and appear only marginally useful in this population. In general, as the initial dose increases, there is a greater and more rapid blood pressure reduction. However, lower initial doses (0.03 to 0.1 µg/kg/min) titrated slowly have been associated with less reflex tachycardia than have higher initial doses (≥ 0.3 µg/kg/min). In clinical trials, doses from 0.01 to 1.6 µg/kg/min have been studied. Most of the effect of a given infusion rate is attained in 15 minutes.

Fenoldopam mesylate injection should be administered by continuous intravenous infusion. A bolus dose should not be used. Hypotension and rapid decreases of blood pressure should be avoided. The initial dose should be titrated upward or downward, no more frequently than every 15 minutes (and less frequently as goal pressure is approached) to achieve the desired therapeutic effect. The recommended increments for titration are 0.05 to 0.1 µg/kg/min.

Use of a calibrated, mechanical infusion pump is recommended for proper control of infusion rate during fenoldopam mesylate injection infusion. In clinical trials, fenoldopam mesylate injection treatment was safely performed without the need for intra-arterial blood pressure monitoring; blood pressure and heart rate were monitored at frequent intervals, typically every 15 minutes. Frequent blood pressure monitoring is recommended.

Use of beta-blockers in conjunction with fenoldopam mesylate injection has not been studied in hypertensive patients and, if possible, concomitant use should be avoided. If the drugs are used together, caution should be exercised because unexpected hypotension could result from beta-blocker inhibition of the reflex response to fenoldopam mesylate injection.

The fenoldopam mesylate injection infusion can be abruptly discontinued or gradually tapered prior to discontinuation. Oral antihypertensive agents can be added during fenoldopam mesylate injection infusion or following its discontinuation. Patients in controlled clinical trials have received intravenous fenoldopam mesylate injection for as long as 48 hours.

PREPARATION OF INFUSION SOLUTION

WARNING: CONTENTS OF AMPOULES MUST BE DILUTED BEFORE INFUSION. EACH AMPOULE IS FOR SINGLE USE ONLY.

Dilution:

The fenoldopam mesylate injection ampoule concentrate must be diluted in 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP using the following dilution schedule:

mL of Concentrate (mg of drug)	Added to	Final Concentration
4 mL (40 mg)	1000 mL	40 µg/mL
2 mL (20 mg)	500 mL	40 µg/mL
1 mL (10 mg)	250 mL	40 µg/mL

The drug dose rate must be individualized according to body weight and according to the desired rapidity and extent of pharmacodynamic effect. The following Table provides the calculated infusion volume in mL/min for a range of drug doses and body weights. The infusion should be administered using a calibrated mechanical infusion pump that can accurately and reliably deliver the desired infusion rate.

Table 5

INFUSION RATES (mL/min) TO ACHIEVE A GIVEN DRUG DOSE RATE (µg/kg/min)

	Drug Dose Rate				
Body Weight (kg)	**0.025 µg/kg/min**	**0.05 µg/kg/min**	**0.1 µg/kg/min**	**0.2 µg/kg/min**	**0.3 µg/kg/min**
	Infusion Rates (mL/min)				
40	0.025	0.05	0.10	0.20	0.30
50	0.031	0.06	0.13	0.25	0.38
60	0.038	0.08	0.15	0.30	0.45
70	0.044	0.09	0.18	0.35	0.53
80	0.050	0.10	0.20	0.40	0.60
90	0.056	0.11	0.23	0.45	0.68
100	0.063	0.13	0.25	0.50	0.75
110	0.069	0.14	0.28	0.55	0.83
120	0.075	0.15	0.30	0.60	0.90
130	0.081	0.16	0.33	0.65	0.98
140	0.088	0.18	0.35	0.70	1.05
150	0.094	0.19	0.38	0.75	1.13

The diluted solution is stable under normal ambient light and temperature conditions for at least 24 hours. Diluted solution that is not used within 24 hours of preparation should be discarded. Parenteral products should be inspected visually. If particulate matter or cloudiness is observed, the drug should be discarded.

HOW SUPPLIED

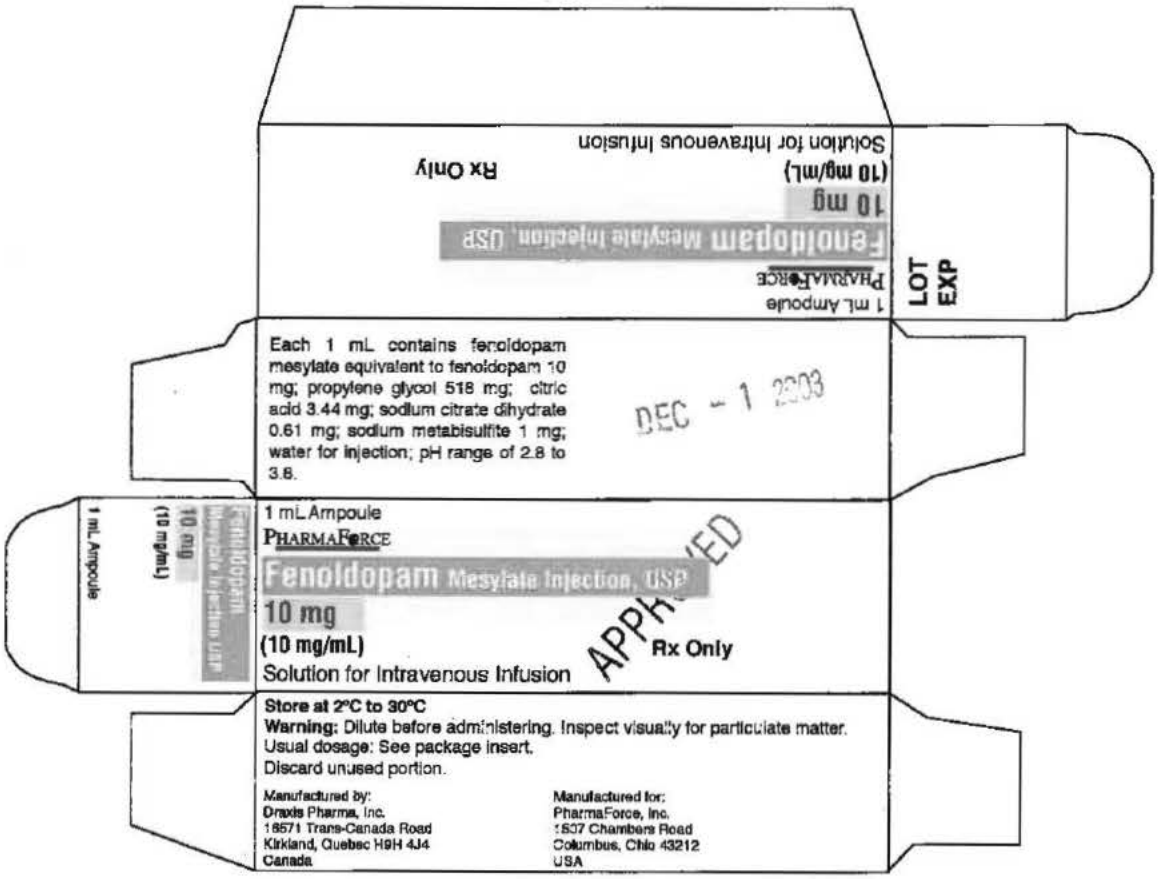
10 mg/mL in 1-mL single-dose ampoules, individually cartoned.
10 mg/mL in 2-mL single-dose ampoules, individually cartoned.

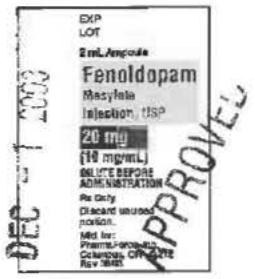
Store at 2°C to 30°C.

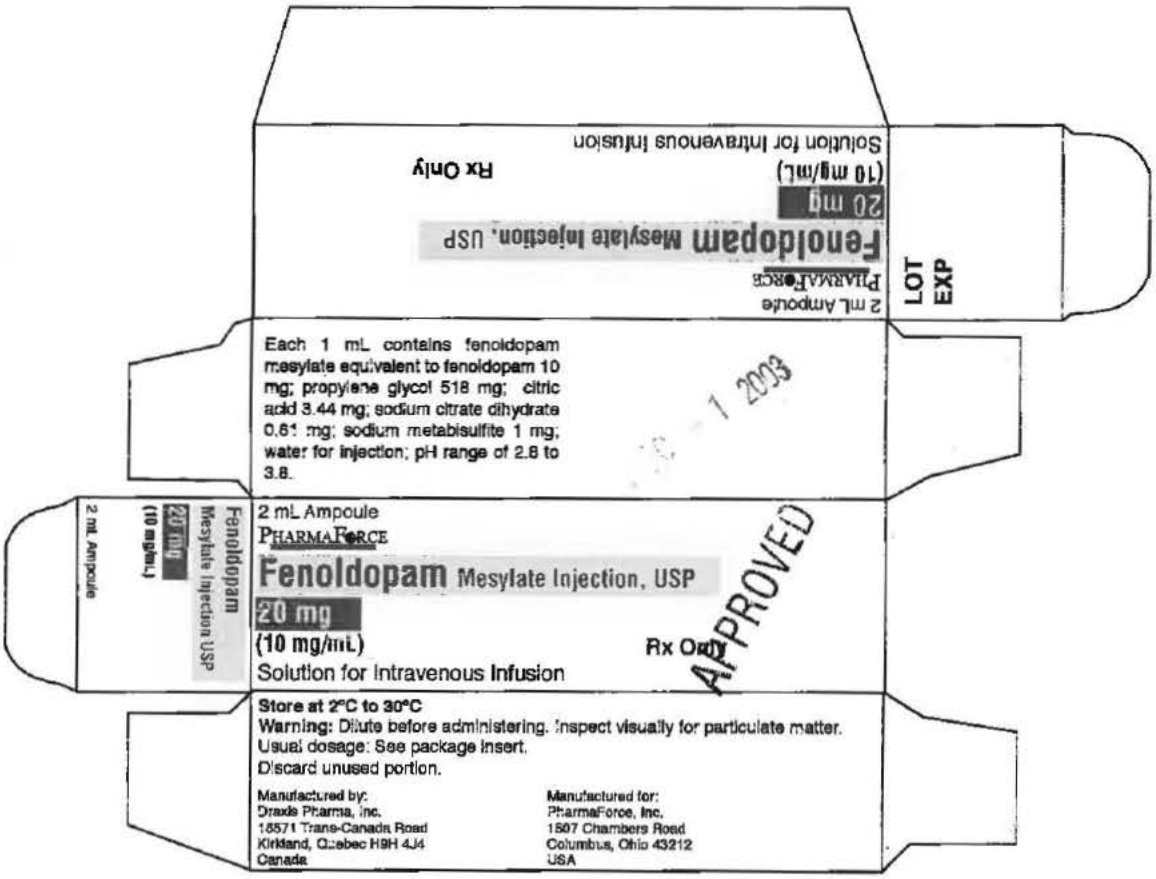
Manufactured by:
Draxis Pharma Inc.
16751 Trans-Canada Road
Kirkland, Quebec H9H 4J4
Canada

Manufactured for:
PharmaForce, Inc.
1507 Chambers Road
Columbus, OH 43212
USA

Revised August 2003


Solution for Intravenous Infusion
Rx Only
(10 mg/mL)
10 mg
Fenoldopam Mesylate Injection USP
PHARMAFORCE
1 mL Ampoule
LOT
EXP
Each 1 mL contains fenoldopam mesylate equivalent to fenoldopam 10 mg; propylene glycol 518 mg; citric acid 3.44 mg; sodium citrate dihydrate 0.61 mg; sodium metabisulfite 1 mg; water for injection; pH range of 2.8 to 3.8.
DEC - 1 2003
1 mL Ampoule
PHARMAFORCE
Fenoldopam Mesylate Injection, USP
10 mg
(10 mg/mL)
Solution for Intravenous Infusion
APPROVED
Rx Only
Store at 2°C to 30°C
Warning: Dilute before administering. Inspect visually for particulate matter.
Usual dosage: See package insert.
Discard unused portion.
Manufactured by:
Draxis Pharma, Inc.
16571 Trans-Canada Road
Kirkland, Quebec H9H 4J4
Canada
Manufactured for:
PharmaForce, Inc.
1537 Chambers Road
Columbus, Ohio 43212
USA


EXP
LOT
2 mL Ampoule
Fenoldopam
Mesylate
Injection, USP
20 mg
(10 mg/mL)
DILUTE BEFORE
ADMINISTRATION
Rx Only
Discard unused
portion.
DEC 1 2003
APPROVED


Fenoldopam Mesylate Injection, USP
20 mg
(10 mg/mL)
Solution for Intravenous Infusion
Rx Only
2 mL Ampoule
PHARMAFORCE
Each 1 mL contains fenoldopam mesylate equivalent to fenoldopam 10 mg; propylene glycol 518 mg; citric acid 3.44 mg; sodium citrate dihydrate 0.61 mg; sodium metabisulfite 1 mg; water for injection; pH range of 2.8 to 3.8.
APPROVED
1 2003
Store at 2°C to 30°C
Warning: Dilute before administering. Inspect visually for particulate matter.
Usual dosage: See package insert.
Discard unused portion.
Manufactured by:
Draxis Pharma, Inc.
16571 Trans-Canada Road
Kirkland, Quebec H9H 4J4
Canada
Manufactured for:
PharmaForce, Inc.
1507 Chambers Road
Columbus, Ohio 43212
USA
LOT
EXP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

LABELING REVIEWS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-656
Date of Submission: May 15, 2003 **AND** August 4, 2003
Applicant's Name: PharmaForce, Inc
Established Name: Fenoldopam Mesylate Injection USP, 10 mg/mL

Approval Summary

1. **CONTAINER – 1 mL and 2 mL single-dose ampoules**
   Satisfactory in **final print** as of the August 4, 2003 submission
   (See blue jacket volume 2.1)

2. **CARTON**
   Satisfactory in **final print** as of the August 4, 2003 submission
   (See blue jacket volume 2.1)

3. **PACKAGE INSERT**
   Satisfactory in **final print** as of the August 4, 2003 submission
   (See blue jacket volume 2.1)

4. **Patent Data – NDA 19-922**

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database	N/A	None

Exclusivity Data– NDA 19-922

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database	N/A	None

5. **Revisions needed post-approval**; None

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Corlopam®
NDA Number: 19-922
NDA Drug Name: Corlopam®
NDA Firm: ; N 19-922, Approved December 15, 1997.
Date of Approval of NDA Insert and supplement: December 15, 1997; NDA 19-922
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Corlopam®
Basis of Approval for the Carton Labeling: Most recently approved labeling of the reference listed drug, Corlopam®

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	

Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
			X

Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence issues: (Compare bioequivalency values: Insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. Labeling was recently approved on December 15, 1997 for the RLD.

2. **Patent/ Exclusivities:**

Patent Data – NDA 19-922

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	***None***	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-922

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:
   NDA: Store at 2° to 30°C.
   ANDA: Store at 2° to 30°C.

(b) (4)

4. Product Line.
   The innovator markets their product in two ampule sizes. 1 mL and 2 mL ampules utilizing the concentration of 10mg/mL.

   The applicant proposes to market their product in 1 mL and 2 mL ampoules utilizing the 10 mg/mL concentration as well.

5. Inactive Ingredients.
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** 0155, Vol. A. 1.1.

6. Container/Closure(See pages 2309 and 2343 in Vol. A.. 1.4)
   Containers: 1 mL and 2 mL Type 1 glass container

7. All manufacturing will be done by Draxis Pharma, Inc for PharmaForce, Inc (See pg. 1190 in vol. A. 1.4)

Date of Review: 8/20/03 Date of Submission: 5/15/03 and 8/4/03

Primary Reviewer: Jim Barlow Date: 8/20/03

Team Leader: John Grace Date: John G Thru 8/21/2003

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cc:

ANDA: 76-656
DUP/DIVISION FILE
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-656
Date of Submission:	January 31, 2003
Applicant's Name:	PharmaForce, Inc.
Established Name:	Fenoldopam Mesylate Injection USP, 10 mg/mL

Labeling Deficiencies:

1. **CONTAINER – 1 mL and 2 mL single-dose ampoules**
   a. Front Panel: Revise your expression of strength format to be the same as the RLD. The RLD has expressed the total drug contents and the concentration with the total drug contents in the color differentiation boxes as follows -

   20 mg
   (10 mg/mL)

   AND

   10mg
   (10 mg/mL)

   b. Relocate the " Dilute before administration" statement directly beneath the expression of strength on the front panel of the label -

   xxmg
   (xx mg/mL)

   DILUTE BEFORE ADMINISTRATION
   Rx only

   c. Please revise to include the statement "Discard unused portion" on your labels.

2. **CARTON**
   See comments 1.(a.) and 1.(c.) listed above for requested revisions.

3. **PACKAGE INSERT**

   a. INDICATIONS AND USAGE
   Fenoldopam mesylate injection...

   b. DOSAGE AND ADMINISTRATION
   Substitute "fenoldopam" throughout the text with "fenoldopam mesylate injection"

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR. Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. Labeling was recently approved on December 15, 1997 for the RLD.

2. Patent/ Exclusivities:

Patent Data – NDA 19-922

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	*None*	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-922

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database	N/A	None

3. Storage/Dispensing Conditions:
   NDA: Store at 2° to 30°C.
   ANDA: Store at 2° to 30°C.

(b) (4)

4. Product Line:
   The innovator markets their product in two ampule sizes. 1 mL and 2 mL ampules utilizing the concentration of 10mg/mL.

   The applicant proposes to market their product in 1 mL and 2 mL ampoules utilizing the 10 mg/mL concentration as well.

5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** 0155, Vol. A. 1.1.

6. Container/Closure(See pages 2309 and 2343 in Vol. A.. 1.4)
   Containers: 1 mL and 2 mL Type 1 glass container

7. All manufacturing will be done by Draxis Pharma, Inc for PharmaForce, Inc (See pg. 1190 in vol. A. 1.4)

Date of Review: 4/4/03 Date of Submission: 1/31/03
Primary Reviewer: Jim Barlow Date: 4/7/03

Team Leader: John Grace Date:

John D Grace 4/28/2003

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cc:

ANDA 76-656
DUP/DIVISION FILE
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

CHEMISTRY REVIEWS

ANDA 76-656

Fenoldopam Mesylate Injection USP, 10mg (base)/1ml and 20mg (base)/2ml

PharmaForce, Inc.

Rosario D'Costa
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-656

2. REVIEW #: 2

3. REVIEW DATE: 09/22/03

4. REVIEWER: Rosario D'Costa

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	01/31/03
Gratuitous Amendment	05/15/03
Acceptable for Filing	02/05/03

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	09/23/03
Minor Amendment	08/01/03

7. NAME & ADDRESS OF APPLICANT:

Name: PharmaForce, Inc.
Address: 1507 Chambers Road
Columbus, OH 43212

Representative: Marilyn Friedly

Telephone: 614-486-7360

Fax: 614-486-9029

8. DRUG PRODUCT NAME/CODE/TYPE:
   Fenoldopam Mesylate Injection, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA
   Paragraph II Certification: The basis for submission is the approved listed drug Corlopam® Fenoldopam Mesylate Injection USP, the subject of NDA #19-922 held by Abbott Hospital Products a division of Abbott Laboratories. PharmaForce certifies that in its opinion and to the best of its knowledge, no unexpired patents exist for Corlopam® Fenoldopam Mesylate Injection USP, the subject of NDA #19-922 held by Abbott Hospital Products a division of Abbott Laboratories. The drug product is not subject to exclusivity determination (Section III of the application). New Chemical Entity (NCE) exclusivity expired September 23, 2002.

10. PHARMACOL. CATEGORY: Hypertension

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg (base)/ml

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X_Rx ___OTC

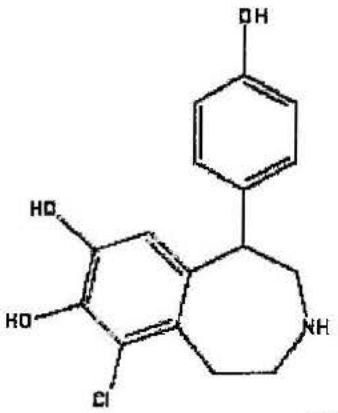
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    _____SPOTS product – Form Completed

    _X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Generic Name: Fenoldopam Mesylate
Chemical Name: 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-[1 *H*]-3-benzazepine-7,8-diol methanesulfonate
Formula: $C_{16}H_{16}ClNO_3.CH_3SO_3H$
Molecular weight: 401.87
CAS registry number(s): 67227-57-0
Hypertension
Chemical Structure:



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17. RELATED/SUPPORTING DOCUMENTS: None

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	10/22/03	Reviewed by RD'Costa
	III			4			
9255	V	Draxis Pharma	Drug Product Manufacturing	4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: **Approvable**

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	09/22/03	N. Nath
EES	Acceptable	03/26/03	J.D. Ambrogio
Methods Validation	N/A		
Labeling	Acceptable	08/21/03	J. Barlow
Bioequivalence	Acceptable	08/28/03	D. Patel
EA	Categorical Exclusion Requested (Satisfactory)	07/29/03	
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-656

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is satisfactory in areas of manufacturing and controls and is therefore recommended for fully "approvable". The associated disciplines of Microbiological process, labeling, bioequivalence and cGMP facility compliance are all satisfactory. There are no existing patents nor unexpired exclusivities for this drug product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance used to manufacture of the drug product, Fenoldopam Mesylate Injection 10mg/ml, is a white to off-white powder that is (b) (4) (b) (4) formulated with known compendium excipients to form the drug product.

A. The drug product is based on the listed drug Corlopam® Fenoldopam Mesylate Injection USP, the subject of NDA #19-922 held by Abbott Hospital Products a division of Abbott Laboratories. The drug is a rapid-acting vasodilator. It is an agonist for D_1-like dopamine receptors and binds with moderate affinity to $(alpha)_2$ –adrenoreceptors. It has no significant affinity for D_2-like receptors $(alpha)_1$ and (beta) –adrenoreceptors, $5HT_1$ and $5HT_2$ receptors or muscarinic receptors. Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. The product is formulated as a solution to be diluted for intravenous infusion.

B. Description of How the Drug Product is Intended to be Used

The recommended dose 0.1μg/kg/ml is administered by continuous intravenous injection with increments of 0.05μg/kg/ml to 0.1μg/kg/ml after 15 minutes followed by monitoring of blood pressure.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry section is satisfactory in areas of manufacturing and controls and is therefore recommended for fully "approvable". The associated disciplines of Microbiological process, labeling, bioequivalence and cGMP facility compliance are all satisfactory. There are no existing patents nor unexpired exclusivities for this drug product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: RD'Costa, Ph.D. /09/25/03 09/26/3
ChemistryTeamLeaderName/Date: AMueller, Ph.D. /09/25/03 9-26-03
ProjectManagerName/Date: C.Kiester, PM /09/25/03 9/29/03
v:\firmsnz\pharmaforce\ltrs&rev\76656.rev2.doc
F/T by:

C. CC Block

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TYPE OF LETTER: APPROVABLE

Following this page, 4 Pages Withheld in Full as (b)(4)

30. **MICROBIOLOGY:** **Acceptable as of September 22, 2003, N. Nath, Division of Microbiology.**

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS:** N/A

32. **LABELING:** **Acceptable as of August 21, 2003, J. Barlow.**

33. **ESTABLISHMENT INSPECTION:** **Acceptable as of March 26, 2003, J.D. Ambrogio, HFD-322.**

34. **BIOEQUIVALENCE:** **Acceptable as August 28, 2003, D. Patel, Division of Bioequivalence.**

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** **Satisfactory in Review #1.**

ANDA 76-656

Fenoldopam Mesylate Injection USP, 10mg (base)/1ml and 20mg (base)/2ml

PharmaForce, Inc.

Rosario D'Costa
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-656

2. REVIEW #: 1

3. REVIEW DATE: 06/26/03

4. REVIEWER: Rosario D'Costa

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	01/31/03
Gratuitous Amendment	05/15/03
Acceptable for Filing	02/05/03

7. NAME & ADDRESS OF APPLICANT:

Name: PharmaForce, Inc.

Address: 1507 Chambers Road
Columbus, OH 43212

Representative: Marilyn Friedly

Telephone: 614-486-7360

Fax: 614-486-9029

8. DRUG PRODUCT NAME/CODE/TYPE:
   Fenoldopam Mesylate Injection, USP

9. LEGAL BASIS FOR SUBMISSION: FFD & CA
   Paragraph II Certification: The basis for submission is the approved listed drug Corlopam® Fenoldopam Mesylate Injection USP, the subject of NDA #19-922 held by Abbott Hospital Products a division of Abbott Laboratories. PharmaForce certifies that in its opinion and to the best of its knowledge, no unexpired patents exist for Corlopam® Fenoldopam Mesylate Injection USP, the subject of NDA #19-922 held by Abbott Hospital Products a division of Abbott Laboratories. The drug product is not subject to exclusivity determination (Section III of the application).

10. PHARMACOL. CATEGORY: Hypertension

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg (base)/ml

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    _____SPOTS product – Form Completed

    __X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

    Generic Name: Fenoldopam Mesylate

Chemistry Review Data Sheet

Chemical Name: 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-[1 *H*]-3-benzazepine-7,8-diol methanesulfonate

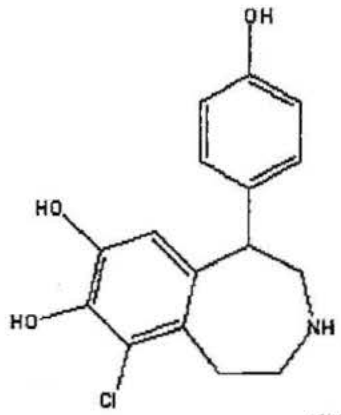
Formula: $C_{16}H_{16}ClNO_3.CH_3SO_3H$

Molecular weight: 401.87

CAS registry number(s): 67227-57-0

Hypertension

Chemical Structure:



CH_3SO_3H

17. RELATED/SUPPORTING DOCUMENTS: None

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Inadequate	07/07/03	Reviewed by RD'Costa
	III			4			
9255	V	Draxis Pharma	Drug Product Manufacturing	4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: Not Approvable

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	03/26/03	J.D. Ambrogio
Methods Validation	N/A		
Labeling	Deficiencies	04/28/03	J. Barlow
Bioequivalence	Pending		
EA	Categorical Exclusion Requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-656

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is deficient in areas of manufacturing and controls and is therefore recommended for "not-approvable".

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance used to manufacture of the drug product, Fenoldopam Mesylate Injection 10mg/ml, is a white to off-white powder that is (b) (4) (b) (4) formulated with known compendium excipients to form the drug product.

A. The drug product is based on the listed drug Corlopam® Fenoldopam Mesylate Injection USP, the subject of NDA #19-922 held by Abbott Hospital Products a division of Abbott Laboratories. The drug is a rapid-acting vasodilator. It is an agonist for D_1-like dopamine receptors and binds with moderate affinity to $(alpha)_2$ –adrenoreceptors. It has no significant affinity for D_2-like receptors $(alpha)_1$ and (beta) –adrenoreceptors, $5HT_1$ and $5HT_2$ receptors or muscarinic receptors. Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. The product is formulated as a solution to be diluted for intravenous infusion.

B. Description of How the Drug Product is Intended to be Used

The recommended dose 0.1µg/kg/ml is administered by continuous intravenous injection with increments of 0.05µg/kg/ml to 0.1µg/kg/ml after 15 minutes followed by monitoring of blood pressure.

C. Basis for Approvability or Not-Approval Recommendation

The "not-approvable" recommendation for chemistry is based on the following issues:

- The Drug Master File (b) (4) is deficient. There are some issues in the drug substance that require resolution
- Some issues in the controls of the drug product both for release and stability that need to be resolved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: RD'Costa, Ph.D. /07/16/03
ChemistryTeamLeaderName/Date: AMueller, Ph.D. /07/16/03
ProjectManagerName/Date: C.Kiester, PM /07/16/03
v:\firmsnz\pharmaforce\ltrs&rev\76656n01.r01.doc
F/T by:

C. CC Block

Following this page, 12 Pages Withheld in Full as (b)(4)

The drug substance and the drug product are compendium items, therefore methods validation is not required. The samples are available upon request (Section XVIII, Vol. 1.7 and pages 3031-3032).

32. LABELING: Labeling Deficiencies, J. Barlow, April 28, 2003.

The labeling information that you have provided was reviewed and found to be deficient. The deficiencies found have been communicated to you under a separate cover.

33. ESTABLISHMENT INSPECTION: Acceptable as of March 26, 2003, J.D. Ambrogio, HFD-322.

34. BIOEQUIVALENCE: Pending

The bioequivalence information that you have provided is currently under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

PharmaForce requests a categorical exclusion from requirement of an environmental assessment statement and certifies compliance of all applicable local, state, and federal environmental regulations (Section XIX, Vol. 1.7 and pages 3033-3034).

ANDA: #76-656 APPLICANT: PharmaForce, Inc.

DRUG PRODUCT: Fenoldopam Mesylate Injection USP, 10mg/1ml and 20mg/2mls

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF # (b) (4) was reviewed and found to be inadequate. Please do not respond until the DMF holder has responded to their deficiencies.

2. (b) (4)

3.

4.

5.

6.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide current room temperature stability data.

2. The labeling information that you have provided was reviewed and found to be deficient. The deficiencies found have been communicated to you under a separate cover.

3. The bioequivalence information that you have provided is currently under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

4. The information submitted on sterility is currently under review by our Microbiology team. Any deficiencies found will be communicated to you under separate cover.

5. [redacted] (b) (4)

Sincerely yours,

7/29/03

Rashmikant Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/RD'Costa, Ph.D./07/16/03 7/29/03
HFD-623/Amueller, Ph.D./07/16/03 7-29-03
HFD-617/C. Kiester, PM/07/16/03
F/T by:
V:\FIRMSNZ\PharmaForce\ltrs&rev\76656N01.R01.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review
Review for HFD-620

20 August 2003

ANDA: 76-656

Drug Product Name
Proprietary: N/A
Non-proprietary: Fenoldopam Mesylate Injection USP
Drug Product Classification: Dopamine like receptor agonist.

Review Number: #1

Subject of this Review
Submission Date: January 31, 2003
Receipt Date: February 5, 2003
Consult Date: N/A
Date Assigned for Review: August 18, 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: PharmaForce, Inc.
Address: 1507 Chambers Road, Columbus, OH 43212
Representative: Marilyn A. Friendly
Telephone: 614-486-7360

Name of Reviewer: Nrapendra Nath

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

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Draxis Pharma, Inc.
16751 Trans-Canada Road
Kirkland, Quebec, CANADA

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 10mg/mL; 1mL and 2mL/ampoule; I/V infusion

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Dopamine like receptor agonist.

B. **SUPPORTING/RELATED DOCUMENTS:** Type V DMF 9255 for Draxis Pharma.

C. **REMARKS:** The subject drug product is manufactured at Draxis Pharma facility in Kirkland, Quebec, Canada for the applicant. DMF 9255 by Drexis Pharma was reviewed in support of the ANDA 40-475 (Paddock Laboratories; Dihydroergotamine Mesylate Injection (b) (4) (b) (4) The DMF was found adequate in February 2003.

(b) (4)

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment" section.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -
The subject drug product is manufactured (b) (4)

B. Brief Description of Microbiology Deficiencies -
None.

C. Assessment of Risk Due to Microbiology Deficiencies -
N/A.

III. Administrative

A. Reviewer's Signature Nrapendra N. Nath 9/22/03

B. Endorsement Block Neal J. Sweeney 9/22/03
Microbiologist / Nrapendra Nath
Microbiology Supervisor/ Neal J. Sweeney

C. CC Block
cc:
Original ANDA
HFD- 600/Division File
Field Copy

filename: V:\Microrev\ 76-656 doc

Following this page, 7 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

G. LABELING

The subject drug product is filled in 1mL and 2mL Type I clear glass ampoules as single dose, (b) (4) [redacted]

Label contains warning that the subject drug product must be diluted before use.

Acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-656
Drug Product Name	Fenoldopam Mesylate Injection, USP
Strength	10 mg/mL in 1 mL and 2 mL ampoules
Applicant Name	PharmaForce, Inc.
Address	1507 Chambers Road, Columbus, OH 43212
Submission Date(s)	January 31, 2003
Amendment Date(s)	N/A
Reviewer	Devvrat Patel
File Location	v:\firmsnz\pharmaforce\ltrs&rev\76656W0103.doc

I. Executive Summary

The firm has requested a waiver of *in vivo* bioavailability/bioequivalence study requirements for its fenoldopam mesylate injection, 10 mg/mL in 1 mL and 2 mL ampoules. The reference listed drug product is Corlopam® 10 mg/mL in 1 mL and 2mL ampules manufactured by Abbott (NDA 19922, approval date: 09/23/1997). The active and inactive ingredients in the test and the reference products are qualitatively and quantitatively the same. The test product meets the criteria for a waiver of *in vivo* bioequivalence requirements in accordance with 21 CFR 320.22(b)(1). The application is acceptable.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Fenoldopam Mesylate Injection, USP
Reference Product	Corlopam® Injection
RLD Manufacturer	Abbott
NDA No.	19-922
RLD Approval Date	09/23/1997
Indication	Indicated for short-term (up to 48 hours) management of severe hypertension when rapid reduction of blood pressure is clinically indicated.

B. PK/PD Information

Half-life	Administered as a constant infusion at rates of 0.01 to 1.6 mcg/kg/min, fenoldopam produced steady-state plasma concentrations that were proportional to infusion rates. The elimination half-life was about 5 minutes.
Metabolism	Fenoldopam is primarily eliminated by conjugation, which include methylation, glucuronidation, and sulfation.
Excretion	About 90% of infused fenoldopam is eliminated in urine, and 10% in feces.
Relevant OGD or DBE History	The DBE accepted the following fenoldopam mesylate injection, 10 mg/mL 1 mL and 2 mL vials, ANDA: 76-582, Bedford Labs, submission date: 12/19/2002. The DBE has not received any control documents on this product.
Agency Guidance	N/A
Drug Specific Issues (if any)	N/A

C. Contents of Submission

Study Types	Yes/No?	How many?
Waiver requests	Yes	1

D. Bioanalytical Method Validation N/A

E. In Vivo Studies N/A

F. Formulation

The test product and the RLD formulations are shown below:

Ingredients (mg/per 1 mL)	Fenoldopam Mesylate Injection, 10 mg/mL	Corlopam® 10 mg/mL[1]
Fenoldopam Mesylate, USP	(b) (4) (equivalent to 10 mg base)	10 mg base
Propylene Glycol, USP	518.00 mg	518.00 mg
Citric Acid, USP	(b) (4) (b) (4) (equivalent to 3.44 mg citric acid (b) (4)	3.44 mg
Sodium Citrate Dihydrate, USP	0.61mg	0.61 mg
Sodium Metabisulfite, NF	1.00 mg	1.00 mg
Water for Injection, USP	(b) (4)	qs to 1 mL
(b) (4)		

[1]The formulation was obtained from the product labeling.

Inactive Ingredients in the test formulation are within IIG limits. The test product is considered identical to the RLD product in its active and inactive ingredients.

G. In Vitro Dissolution N/A

H. Waiver Request

The applicant requests a waiver of *in vivo* bioequivalence testing under 21 CFR 320.22(b)(1) for the following strength: 10 mg/mL, in 1 mL and 2 mL ampoules

The test product is a sterile solution intended for intravenous administration. The route of administration, dosage form, and strength of the test product are the same as those of the RLD. The test product is considered identical to the RLD product in its active and inactive ingredients. The test product meets the criteria for a waiver of *in vivo* bioequivalence requirements.

I. Deficiency Comments

None

J. Recommendation

The Division of Bioequivalence agrees that the information submitted by PharmaForce, Inc. demonstrates that its fenoldopam mesylate injection USP, 10 mg/mL in 1 mL and 2 mL ampoules, falls under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that a waiver of *in vivo* bioavailability study requirements may be granted. PharmaForce's fenoldopam mesylate injection, 10 mg/mL in 1 mL and 2 mL ampoules, is deemed bioequivalent to Abbott's Corlopam®, 10 mg/mL in 1 mL and 2 mL ampules.

Devrat Patel 8-20-2003

Devvrat Patel, Pharm.D.
Review Branch II
Division of Bioequivalence

8/27/2003

Shriniwas Nerurkar, Ph.D.
Team Leader
Review Branch II
Division of Bioequivalence
Office of Generic Drugs

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CC: ANDA 76656
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patel

V:\FIRMSNZ\PHARMAFORCE\LTRS&REV\76656W0103.DOC
Printed in final on 08/19/2003

8/27/03

Endorsements: (Final with Dates)
HFD-655/ Patel 8/20/03
HFD-655/ Nerurkar
HFD-650/ D. Conner 8/28/03

BIOEQUIVALENCY - ACCEPTABLE

Submission date:
January 31, 2003

1. **WAIVER** (WAI)

Strengths: 10 mg/mL
Outcome: AC

Outcome Decisions: **AC** - Acceptable
WC - Without charge

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-656 APPLICANT: PharmaForce, Inc.

DRUG PRODUCT: Fenoldopam Mesylate Injection, USP
10 mg/mL in 1 mL and 2 mL ampoules

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76656
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Patel

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Printed in final on 08/19/2003

8/27/03

Endorsements: (Final with Dates)
HFD-655/ Patel 8/20/03
HFD-655/ Nerurkar
HFD-650/ D. Conner 8/28/03

BIOEQUIVALENCY - ACCEPTABLE

Submission date:
January 31, 2003

1. **WAIVER** (WAI)

Strengths: 10 mg/mL
Outcome: AC

Outcome Decisions: **AC** - Acceptable
WC - Without charge

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76656

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-656 Applicant Pharmaforce
Drug Fenoldopam Mesylate Injection Strength 10 mg (base)/ml and 20 mg (base)/2 ml
APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Project Manager, Craig Kiester Review Support Br Team 1	Date 9/20/03 Initials CK	Date Initials

Application Summary:

Original Rec'd date 1/31/03
Date Acceptable for Filing 2/5/03
Patent Certification (type) II
Date Patent/Exclus.expires 9/23/08
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD = ~~123~~ Corlopam Inj
Date checked _____ NDA# 19922
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 3/26/03
Date of Office Bio Review 8/28/03
Date of Labeling Approv. Sum 8/21/03
Date of Sterility Assur. App. 9/22/03
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. Gregg Davis **PPIV ANDAs Only** N/A Deputy Director, DLPS	Date Initials	Date Initials

Contains GDEA certification: Yes ☐ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☐ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Comments:

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

3. Div. Dir./Deputy Dir. Chemistry Div. I Comments:	Date Initials	Date 11/3 Initials PS

(b) (4) [redacted]

Dr Thackeray was notified and agreed

eer Dorcas - OK?

REVIEWER:	DRAFT Package	FINAL Package
4. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review)	Date _____ Initials _____ Satisfactory	Date 11/25/03 Initials JA
5. Peter Rickman Director, DLPS	Date 11/25/2003 Initials _____	Date 11/25/2003 Initials _____

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition:Yes☐ No☐

Comments:

No patents - NCE expired 9/23/2002

1ST Generic - No 180 day exclusivity issues

Office Level Bio acceptable 8/28/2003 waiver granted

Labeling acceptable 8/21/2003

Micro acceptable 9/22/2003

OR EER acceptable 3/26/2003 — OK to approve updated EER acceptable 11/26/2003

5. Robert L. West Deputy Director, OGD	Date _____ Initials _____	Date _____ Initials _____ 11/28

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition:Yes☐ No☐

Comments:

6. Gary Buehler Director, OGD Comments:	Date 12/1/03 Initials GB	Date 12/1/03 Initials GB

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Craig Kiester Review Support Br Team 1	Date 12/1/03 Initials CK	Date _____ Initials _____

12/1 Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

11:20 Time notified of approval by phone 11:20 Time approval letter faxed

FDA Notification:

12/1/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

12/1/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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Mueller, Albert J

From: Throckmorton, Douglas C
Sent: Tuesday, November 04, 2003 7:25 AM
To: Mueller, Albert J
Cc: Lunn, George; Patel, Hasmukh B; Holcombe Jr, Frank O; Patel, Rashmikant M; Schwartz, Paul; Kiester, Craig; D'Costa, Rosario; Srinivasachar, Kasturi
Subject: RE: First Generic Approval of Fenoldopam Mesylate Injection USP

(b) (4)

DCT

-----Original Message-----
From: Mueller, Albert J
Sent: Monday, November 03, 2003 2:56 PM
To: Throckmorton, Douglas C
Cc: Lunn, George; Patel, Hasmukh B; Holcombe Jr, Frank O; Patel, Rashmikant M; Schwartz, Paul; Kiester, Craig; D'Costa, Rosario
Subject: First Generic Approval of Fenoldopam Mesylate Injection USP

Gentlemen,

(b) (4)

We have recently completed review of the first generic Fenoldopam Mesylate Injection drug product and are proceeding with its approval in the Office of Generic Drugs. (b) (4)

We feel that we can go ahead and proceed with the approval process for this ANDA for the following reasons: 1) at the present time, the DMF holder has submitted sufficient information (b) (4)
(b) (4)
.

We look forward to your comments and would appreciate your input prior to any approval action on our part.

Regards,

Al Mueller, Team Leader
CDER/OGD, DC1/Team 1

APPEARS THIS WAY ON ORIGINAL

Gaj

AUG 28 2003

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-656

SPONSOR : PharmaForce, Inc.

DRUG AND DOSAGE FORM : Fenoldopam Mesylate Injection, USP

STRENGTH(S) : 10 mg/mL, in 1 mL and 2 mL ampoules

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : The proposed product is a parenteral solution for administration by intravenous infusion after dilution. The active and inactive ingredients in the test and the reference products are qualitatively and quantitatively the same. A waiver of *in vivo* bioavailability/bioequivalence study requirements based on 21 CFR 320.22(b)(1) is granted.

DISSOLUTION : N/A

DSI INSPECTION STATUS

nspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Devvrat Patel, Pharm.D. BRANCH : II

INITIAL : DP DATE : 8/20/2003

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH : II

INITIAL : DNamuh DATE : 8/27/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 8/28/03

Nerurkar, Shriniwas G

From: Conner, Dale P
Sent: Wednesday, August 20, 2003 1:59 PM
To: Nerurkar, Shriniwas G
Subject: RE: REVIEW 76656 Pharmaforce Fenoldopam inj Dev 1-31-03

OK

DALE

1. REVIEW — SIGNED BY DEV & VIJAY
2. SIGN-OFF SHEET — DEV, VIJAY & DALE
3. LETTER - DALE

-----Original Message-----
From: Nerurkar, Shriniwas G
Sent: Wednesday, August 20, 2003 10:16 AM
To: Conner, Dale P
Subject: RE: REVIEW 76656 Pharmaforce Fenoldopam inj Dev 1-31-03

Dale:

Since it was not a simple waiver for an injection, ANDA 76619 was sent to you.
Barbara has reviewed and signed the ANDA 76619.
I sent 40530 only yesterday.
It should not have been sent because it is a simple waiver for an injection.

Thanks.

Vijay

-----Original Message-----
From: Conner, Dale P
Sent: Wednesday, August 20, 2003 9:53 AM
To: Nerurkar, Shriniwas G
Subject: RE: REVIEW 76656 Pharmaforce Fenoldopam inj Dev 1-31-03

Vijay:

Do you mean 76619 for XJ's review? Or is there another one?

Dale

-----Original Message-----
From: Nerurkar, Shriniwas G
Sent: Wednesday, August 20, 2003 9:44 AM
To: Conner, Dale P; Davit, Barbara M
Cc: Patel, Devvrat
Subject: RE: REVIEW 76656 Pharmaforce Fenoldopam inj Dev 1-31-03

Dale and Barbara:

I stand corrected.
There is also a similar review (40530) from XJ that was sent to you by mistake.
I shall amend both reviews and send them for your signature.
Thanks.

Vijay

-----Original Message-----
From: Conner, Dale P
Sent: Wednesday, August 20, 2003 9:27 AM
To: Nerurkar, Shriniwas G; Davit, Barbara M
Cc: Patel, Devvrat
Subject: RE: REVIEW 76656 Pharmaforce Fenoldopam inj Dev 1-31-03

Vijay:

MINOR AMENDMENT

ANDA 76-656

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 29 2003

APPLICANT: Pharmaforce, Inc.

TEL: 614.486.7360

ATTN: Marilyn Friedly

FAX: 614.486.9029

FROM: Craig Kiester

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated January 31, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fenoldopam Mesylate Injection, USP.

Reference is also made to your amendment(s) dated: May 15, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

Cr 10/29/03

JUL 2 9 2009

ANDA: #76-656 APPLICANT: PharmaForce, Inc.

DRUG PRODUCT: Fenoldopam Mesylate Injection USP, 10mg/1ml and 20mg/2mls

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The DMF # (b) (4) was reviewed and found to be inadequate. Please do not respond until the DMF holder has responded to their deficiencies.

2. (b) (4)

3.

4.

5.

6.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide current room temperature stability data.

2. The labeling information that you have provided was reviewed and found to be deficient. The deficiencies found have been communicated to you under a separate cover.

3. The bioequivalence information that you have provided is currently under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

4. The information submitted on sterility is currently under review by our Microbiology team. Any deficiencies found will be communicated to you under separate cover.

5. [redacted] (b) (4)

Sincerely yours.

Rashmikant Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA# 76-656 **FIRM NAME** PHARMAFORCE, INC.

RELATED APPLICATION(S) NA **FIRST GENERIC?** NA

DRUG NAME: FENOLDOPAM MESYLATE
DOSAGE FORM: INJECTION USP, EQ 10 MG BASE/ML

Electronic Submission: NA E-mail notification sent: NA Comments: NA

Random Assignment Queue: Random 1 Chem Team Leader: Mueller, Al PM: Keister, Craig

Labeling Reviewer: Barlow, Jim Micro Review: YES PD study (Med Ofcr): NA

Letter Date JANUARY 31, 2003	**Received Date** FEBRKUARY 5, 2003
Comments EC 1 YES **On Cards YES** **HYPERTENSIVE AGENTS**	**Therapeutic Code 1020100 ANTI-**
Methods Validation Package (3 copies) (Required for Non-USP drugs) YES---Fenoldpam Mesylate Injection USP, page 724	
Archival, and Review copies Field Copy Certification (Original Signature) YES	
Cover Letter YES	
Table of Contents YES	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) RX YES	☒
Sec. II	**Basis for Submission** **NDA: 19-922** RLD: CORLOPAM Firm: ABBOTT ANDA suitability petition required? If yes, consult needed for pediatric study requirement.	☒
Sec. III	**Patent Certification** 1. Paragraph: II 2. Expiration of Patent: YES A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement YES**	☒

Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use 2. Active ingredients 3. Route of administration 4. Dosage Form 5. Strength	☒
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL 2. How supplied: 10 mg/mL-- 1mL + 2 mL ampoules 2. 1 RLD label and 1 RLD container label 3. 1 side by side labeling comparison with all differences annotated and explained	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NA **2. Request for Waiver of In-Vivo Study(ies):** YES---bio-waiver (Q1vsQ2 ok) **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** 5. **Study Type:** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted c. In-Vitro Dissolution	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. Data Files (Computer Media) Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation 2. Inactive ingredients as appropriate	☐
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers b. Type II DMF authorization letters or synthesis NO-firm states application contains all synthesis information. Ok with chemistry. c. COA(s) specifications and test results from drug substance mfgr(s) d. Applicant certificate of analysis e. Testing specifications and data from drug product manufacturer(s) f. Spectra and chromatograms for reference standards and test samples g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified b. Testing specifications (including identification and characterization) c. Suppliers' COA (specifications and test results) d. Applicant certificate of analysis	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) 2. CGMP Certification 3. CFN numbers	☒

Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including MicrobiologicalValidation, if Appropriate) 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) [redacted] (b) (4) 3.If sterile product: [redacted] (b) (4) 4.Filter validation (if aseptic fill) 5. Reprocessing Statement	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation 2. lot: [redacted] (b) (4) 2. In-process Controls - Specifications and data	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) 2. Components Specification and Test Data (Type III DMF References) 3. Packaging Configuration and Sizes 4. Container/Closure Testing 5. Source of supply and suppliers address	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data 2. Certificate of Analysis for Finished Dosage Form	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted 2. Post Approval Commitments 3. Expiration Dating Period 4. Stability Data Submitted a. 3 month accelerated stability data b. Batch numbers on stability records the same as the test batch	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	☒
Sec. XVII	**Environmental Impact Analysis Statement**	☒

Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature) YES 3. List of Convictions statement (original signature)	☒

Reviewing CSO/CST Paras Patel **Date** 3/10/03	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 12-MAR-2003
Duplicate copy sent to bio: (Hold if RF and send when acceptable)	
Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Review filter validation data with micro

OGD Form Revised 11/30/2001
MSWord Template revised: 8/7/2002

ANDA 76-656

PharmaForce, Inc.
Attention: Marilyn A. Friedly
1507 Chambers Road
Columbus, OH 43212

MAR 12 2003

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Fenoldopam Mesylate Injection USP, 10 mg(base)/mL, 1 mL and 2 mL ampoules

DATE OF APPLICATION: January 31, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 5, 2003

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Craig Kiester
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-656
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis,Chief RSB 12-MAR-2003 date
HFD-615/PPatel,CSO date 3/11/03
Word File
V:\Firmsnz\PharmaForce\ltrs&rev\76656.ACK

F/T
ANDA Acknowledgment Letter!