# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

***APPLICATION NUMBER:***

# ANDA 77826

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

**Sponsor:** Teva Parenteral Medicines Inc.

**Approval Date:** March 7, 2007

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-826

SICOR Pharmaceuticals, Inc.
Attention: Sonia Hernandez
Manager, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 29, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fenoldopam Mesylate Injection USP, 10 mg/mL, packaged in 10 mg/1mL and 20 mg/2mL Single Dose Vials.

Reference is also made to your amendments dated May 12, July 20, August 18, August 31, and September 29, 2006.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Fenoldopam Mesylate Injection USP, 10 mg/mL, packaged in 10 mg/1mL and 20 mg/2mL Single Dose Vials to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Corlopam Injection USP, 10 mg/mL, packaged in 10 mg/1mL and 20 mg/2mL Single Dose Vials , respectively, of Hospira, Inc.

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

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these

submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-826
Division File
Field Copy
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HFD-013
HFD-610/Orange Book Staff

Approved Electronic Labeling Located at:
\\CDSESUB1\N77826\N_000\2006-05-12\SICOR Fenoldopam Mesylate Injection, USP 8211-01 vial.pdf

\\CDSESUB1\N77826\N_000\2006-05-12\SICOR Fenoldopam Mesylate Injection, USP 8221-01 vial.pdf

Endorsements:
HFD-620/Y.Amin/ 11/27/06
HFD-623/A.Mueller/ 9/18/06 11-15-06
HFD-617/S.Eng/
HFD-613/J.Barlow/ > see emails
HFD-613/J.Grace/

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SICOR

F/T by se

APPROVAL

EER labeling comments dtd 11/2 9/12

Robert West
3/1/2007
EES is now acceptable.

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

# LABELING

**PACKAGE INSERT** **Rx Only**

**FENOLDOPAM MESYLATE INJECTION, USP**

**10 mg/mL**

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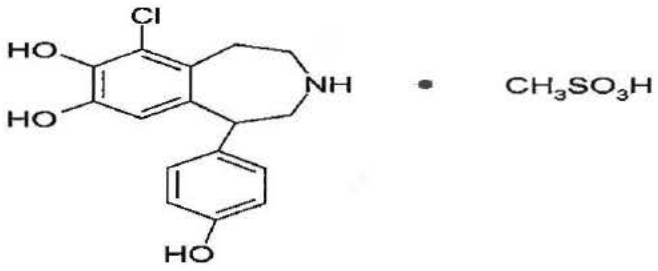
**Rx ONLY**

## 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-7,8-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 $C_{17}H_{20}ClNO_6S$. It is sparingly soluble in water, ethanol and methanol, and is soluble in propylene glycol.

Vial: Each mL contains: Own information

## 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 $\alpha_2$-adrenoceptors. It has no significant affinity for $D_2$-like receptors, $\alpha_1$ and $\beta$ 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 $\alpha$- or $\beta$-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.

### Pharmacokinetics

**Adult Patients:**

Fenoldopam, administered as a constant infusion at rates of 0.01 to 1.6 mcg/kg/min, 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.

The pharmacokinetics of fenoldopam were not influenced by age, gender, or race in adult patients with a hypertensive emergency. There have been no formal drug-drug interaction studies using intravenous fenoldopam.

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.

**Pediatric Patients:** Information related to the pharmacokinetics of fenoldopam injection in pediatric patients is approved for Hospira Inc.'s fenoldopam drug products. However, due to Hospiras marketing exclusivity rights, this drug product is not labeled for pediatric use.

In radio labeled studies in rats, no more than 0.005% of fenoldopam crossed the blood-brain barrier.

**Excretion and Metabolism**

Radio labeled 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.

**Pharmacodynamics and Clinical Studies**

**Adult Patients:**

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 154/98 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 1 shows the results of the study. The onset of response was rapid at all infusion rates, with the 15-minute response representing 50-100% 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 mcg/kg/min than to 0.4 mcg/kg/min.

**Table 1**

**PHARMACODYNAMIC EFFECTS OF FENOLDOPAM IN MILD TO MODERATE ADULT HYPERTENSIVE PATIENTS**

| Time Point and Mean Change from Time Zero ± SE | Infusion Rate (mcg/kg/min) | | | | |
|---|---|---|---|---|---|
| | 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 | -6 ± 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 | +18 ± 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 ± 8 | -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 ± 6 | -22 ± 8 | -9 ± 6 | -14 ± 10 |
| Diastolic BP | -9 ± 5 | -10 ± 6 | -9 ± 7 | -9 ± 2 | -9 ± 3 |
| Heart rate | +1 ± 2 | 0 ± 4 | +1 ± 4 | +12 ± 3 | +8 ± 3 |

* Mean change form 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 mcg/kg/min for up to 24 hours to 94 adult 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 2**).

**Table 2**

**PHARMACODYNAMIC EFFECTS OF FENOLDOPAM IN HYPERTENSIVE ADULT EMERGENCY PATIENTS**

| Time Point and Pharmacodynamic Parameters | Infusion Rate mcg/kg/min | | | |
|---|---|---|---|---|
| | 0.01<br>N = 25 | 0.03<br>n = 24 | 0.1<br>n = 22 | 0.3<br>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 form baseline ± S.E.

Two hundred and thirty six severly 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 mcg/kg/min; for nitroprusside, the dose ranged from 1.0 to 8.0 mcg/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 for evaluation).

**Pediatric Patients:** Information related to the pharmacodynamics of fenoldopam injection in pediatric patients is approved for Hospira Inc's fenoldopam drug products. However, due to Hospiras marketing exclusivity rights, this drug product is not labeled for pediatric use.

## INDICATIONS AND USAGE

**Adult Patients:**

Fenoldopam Mesylate Injection, USP 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.

**Pediatric Patients:** Information related to the indicated use of fenoldopam injection in pediatric patients is approved for Hospira Inc's fenoldopam drug products. However, due to Hospiras marketing exclusivity rights, this drug product is not labeled for pediatric use.

## CONTRAINDICATIONS

None known.

## WARNINGS

**Use of beta-blockers in conjunction with fenoldopam 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.**

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 – 33.0 mm Hg), infusion of fenoldopam at escalating doses ranging from 0.05 – 0.5 mcg/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 Mesylate Injection, USP administration to patients with glaucoma or intraocular hypertension should be undertaken with caution.

**Tachycardia**: Fenoldopam causes a dose-related tachycardia (**Table 1** and **Table 2**), particularly with infusion rates above 0.1 mcg/kg/min.

Tachycardia in adults diminishes over time but remains substantial at higher doses. Tachycardia in pediatric patients at doses > 0.8 mcg/kg/min persist at least for 4 hours.

**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.

In pediatric patients, fenoldopam was only administered to patients with an indwelling intraarterial line.

**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.

**Intracranial pressure:** The effect of fenoldopam in the presence of increased intracranial pressure has not been studied.

**Drug interactions with Beta-Blockers:** Concomitant use of fenoldopam with beta-blockers should be avoided. If the drugs are used together, caution should be exercised because unexpected hypotension could result from beta-blocker inhibition of the sympathetic reflex response to fenoldopam.

**Drug Interactions**: **General**: 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 209 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.

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 chromosomal 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**: **Teratogene Effects:** *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:** Clinical study information related to the safety and effectiveness of fenoldopam injection in pediatric patients ages < 1 month to 12 years old is approved by Hospira Inc's fenoldopam drug product. However, due to Hospiras marketing exclusivity rights, this drug product, is not labeled for pediatric use.

**Geriatric use:** Clinical studies of fenoldopam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## ADVERSE REACTIONS

**Adult Patients:**

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 adult 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 3**

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

| Body System | Event | Fenoldopam Doses (mcg/kg/min) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Placebo (n = 7) | 0.01 (n = 26) | 0.03 – 0.04 (n = 31) | 0.1 (n = 28) | 0.3 – 0.4 (n = 29) | 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 | 2 |
| | 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 adult patients and not listed in Table 3 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 |
| Hematologic/Lymphatic: | leukocytosis, bleeding |
| Respiratory: | dyspnea, upper respiratory disorder |
| Genitourinary: | Oliguria |
| Musculoskeletal: | limb cramp |

**Pediatric Patients:** Information relating to treatment-emergent adverse events is approved for Hospira Inc.'s fenoldopam injection drug products. However, due to hospiras marketing exclusivity rights, this drug product is not labeled for pediatric use.

## 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 mcg/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 involes activation of $D_1$-like dopaminergic receptors. Such lesions have not been seen in dogs given doses up to 100 mcg/kg/min by continuous intravenous infusion for 24 hours, nor were they seen in dogs infused at the same dose for 6 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

**Adult Patients:**

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, USP dose may be chosen from Tables 1 and 2 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 mcg/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 – 0.1 mcg/kg/min) titrated slowly have been associated with less reflex tachycardia than have higher initial doses (≥0.3 mcg/kg/min). In clinical trials, doses from 0.01 – 1.6 mcg/kg/min have been studied. Most of the effect of a given infusion rate is attained in 15 minutes.

Fenoldopam Mesylate Injection, USP 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 – 0.1 mcg/kg/min.

Use of a calibrated, mechanical infusion pump is recommended for proper control of infusion rate during Fenoldopam Mesylate Injection, USP infusion. In clinical trials, fenoldopam 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.

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

**PREPARATION OF INFUSION SOLUTION**

**WARNING: CONTENTS OF AMPULES MUST BE DILUTED BEFORE INFUSION. EACH AMPULE IS FOR SINGLE USE ONLY.**

**Dilution:**

**Adult Patients:**

The Fenoldopam Mesylate Injection, USP ampule 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 mcg/mL |
| 2 mL (20 mg) | 500 mL | 40 mcg/mL |
| 1 mL (10 mg) | 250 mL | 40 mcg/mL |

The drug dose rate must be individualized according to body weight and according to the desired rapidity and extent of pharmacodynamic effect. Table 4 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.

**Infusion rate:**

**Table 4**

**FENOLDOPAM ADULT INFUSION RATES (mL/hour)**
**DRUG DOSAGE FOR ADULTS > 40 KG, USING 40 MCG/ML CONCENTRATION**
**NOTE: CONCENTRATION IS DIFFERENT FROM PEDIATRIC PATIENTS, SEE BELOW:**
**PEDIATRIC PATIENTS**

| Body Weight (kg) | Infusion Rate | | | | |
|---|---|---|---|---|---|
| | 0.025 mcg/kg/min | 0.05 mcg/kg/min | 0.1 mcg/kg/min | 0.2 mcg/kg/min | 0.3 mcg/kg/min |
| 40 | Infusion Rates (mL/hour) of 40 mcg/mL solution | | | | |
| 50 | 1.5 | 3 | 6 | 12 | 18 |
| 60 | 1.9 | 3.8 | 7.5 | 15 | 22.5 |
| | 2.3 | 4.5 | 9.0 | 18 | 27 |
| 70 | 2.6 | 5.3 | 10.5 | 21 | 31.5 |
| 80 | 3 | 6 | 12 | 24 | 36 |
| 90 | 3.4 | 6.8 | 13.5 | 27 | 40.5 |
| 100 | 3.8 | 7.5 | 15 | 30 | 45 |
| 110 | 4.1 | 8.3 | 16.5 | 33 | 49.5 |
| 120 | 4.5 | 9 | 18 | 38 | 54 |
| 130 | 4.9 | 9.8 | 19.5 | 39 | 58.5 |
| 140 | 5.3 | 10.5 | 21 | 42 | 63 |
| 150 | 5.6 | 11.3 | 22.5 | 45 | 67.5 |

**Table 4 (continuation)**

**FENOLDOPAM ADULT INFUSION RATES (mL/hour)**
**DRUG DOSAGE FOR ADULTS > 40 KG, USING 40 MCG/ML CONCENTRATION**
**NOTE: CONCENTRATION IS DIFFERENT FROM PEDIATRIC PATIENTS, SEE BELOW:**
**PEDIATRIC PATIENTS**

| Body Weight (kg) | Infusion Rate | | | | | |
|---|---|---|---|---|---|---|
| | 0.5 mcg/kg/min | 0.8 mcg/kg/min | 1 mcg/kg/min | 1.2 mcg/kg/min | 1.4 mcg/kg/min | 1.6 mcg/kg/min |
| 40 | Infusion Rates (mL/hour) of 40 mcg/mL solution | | | | | |
| 50 | 30 | 48 | 60 | 72 | 84 | 96 |
| 60 | 37.5 | 60 | 75 | 90 | 105 | 120 |
| | 45 | 72 | 90 | 108 | 126 | 144 |
| 70 | 52.5 | 54 | 105 | 126 | 147 | 168 |
| 80 | 60 | 96 | 120 | 144 | 168 | 192 |
| 90 | 67.5 | 108 | 135 | 162 | 189 | 216 |
| 100 | 75 | 120 | 150 | 180 | 210 | 240 |
| 110 | 82.5 | 132 | 165 | 196 | 231 | 264 |
| 120 | 90 | 144 | 180 | 216 | 252 | 288 |
| 130 | 97.5 | 156 | 195 | 234 | 273 | 312 |
| 140 | 105 | 168 | 210 | 252 | 294 | 336 |
| 150 | 112.5 | 180 | 225 | 270 | 315 | 360 |

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.

**Pediatric Patients:** Information related to the dosing of fenoldopam injection in pediatric patients is approved for Hospira Inc.'s fenoldopam drug products. However, due to Hospiras marketing exclusivity rights, this drug product is not labeled for pediatric use.

**HOW SUPPLIED**

1 mL (10 mg/mL), etc...

2 mL (10 mg/mL), etc....

Store at 2° to 30°C.

Date

Manufactured in
Distributed by

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

# LABELING REVIEWS

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

ANDA Number: 77-826 Date of Submission: September 29, 2006
Applicant's Name: SICOR Pharmaceuticals, Inc.
Established Name: Fenoldopam Mesylate Injection USP, 10 mg/mL

**Approval Summary:**

1. **Do you have final printed labels and labeling? Yes**

2. **CONTAINER – 1 mL and 2 mL single-dose vials**
   Satisfactory in **final print** as of the August 18, 2006 electronic submission
   \\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate Injection, USP 8211-01 vial.pdf
   \\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate Injection, USP 8221-01 vial.pdf

3. **CARTON – 1 mL and 2 mL single-dose**
   Satisfactory in **final print** as of the August 18, 2006 electronic submission
   \\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate Injection, USP 8211-01 carton.pdf
   \\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate injection, USP 8221-01 carton.pdf

4. **PACKAGE INSERT**
   Satisfactory in **final print** as of the September 29, 2006 submission.
   \\CDSESUB1\N77826\N_000\2006-09-29\SICOR Fenoldopam Mesylate Injection, USP PI.pdf

5. **Patent/ Exclusivities:**
   **Patent Data – NDA 19-922**

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| | | 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 |
|---|---|---|---|
| I-422 | INDICATED FOR THE IN-HOSPITAL SHORT-TERM (UP TO 4 HOURS) REDUCTION IN BLOOD PRESSURE IN PEDIATRIC PATIENTS | 4/1/07 | Carved Out and substituted with Pediatric Division/New Drug Division and OGD recommended statements |

6. **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® Injection
NDA Number: 19-922
NDA Drug Name: Corlopam® Injection
NDA Firm: Abbott Laboratories; N 19-922/SE-005; Approved April 1, 2004
Date of Approval of NDA Insert and supplement: Approved April 1, 2004; N 19-922/SE-005
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® Injection.

**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 April 1, 2004 for the RLD. Used recently approved insert and container/carton labeling for ANDA 76-582 (fenoldopam injection) produced by Bedford for guidance. **(NOTE: SPL was submitted with this application on 9/29/06)**
2. Storage/Dispensing Conditions:
   NDA: Store at 2° to 30°C.
   ANDA: Store at 2° to 30°C (b) (4)
   (b) (4)
3. 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 single-use vials utilizing the 10 mg/mL concentration as well.
4. 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** (Section 2.3.P.1, Vol. 1.4 and pages 4007):
5. Container/Closure:

| Drug content/vial | (b) (4) |
|---|---|
| 10 mg Base | |
| 20 mg Base | |

6. All manufacturing will be done by: (b) (4)

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Date of Review: 10/4/06 Date of Submission: 9/29/06

Primary Reviewer: Jim Barlow Date: 10/5/06

Team Leader: John Grace Date: John Grace 10-5-2006

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cc:

ANDA: 77-826
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\SICOR\LTRS&REV\77826apsummary_labeling.doc
Review

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

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| | |
|---|---|
| ANDA Number: | 77-826 |
| Date of Submission: | August 18, 2006 |
| Applicant's Name: | SICOR Pharmaceuticals, Inc. |
| Established Name: | Fenoldopam Mesylate Injection USP, 10 mg/mL |

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**Labeling Deficiencies:**

1. **CONTAINER – 1 mL and 2 mL single-dose vials**
   Satisfactory in **final print** as of the August 18, 2006 electronic submission
   **\\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate Injection, USP 8211-01 vial.pdf**

   **\\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate Injection, USP 8221-01 vial.pdf**

2. **CARTON – 1 mL and 2 mL single-dose**
   Satisfactory in **final print** as of the August 18, 2006 electronic submission
   **\\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate Injection, USP 8211-01 carton.pdf**

   **\\CDSESUB1\N77826\N_000\2006-08-18\SICOR Fenoldopam Mesylate Injection, USP 8221-01 carton.pdf**

3. **PACKAGE INSERT**
   DOSAGE AND ADMINISTRATION

   Adult Patients- First paragraph, second sentence -Revise to read as follows:

   An initial Fenoldopam Mesylate Injection, USP may be chosen from Tables 1 and 2 in the **CLINICAL PHARMACOLOGY** section.....

Please revise your package insert labeling as described above and submit electronically.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2alG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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 April 1, 2004 for the RLD. Used recently approved insert and container/carton labeling for ANDA 77-582 (fenoldopam injection) produced by Bedford for guidance.
2. **Patent/ Exclusivities:**
   **Patent Data – NDA 19-922**

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| | | 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 |
|---|---|---|---|
| I-422 | INDICATED FOR THE IN-HOSPITAL SHORT-TERM (UP TO 4 HOURS) REDUCTION IN BLOOD PRESSURE IN PEDIATRIC PATIENTS | 4/1/07 | Carved Out and substituted with Pediatric Division/New Drug Division and OGD recommended statements |

3. Storage/Dispensing Conditions:
   NDA: Store at 2° to 30°C.
   ANDA: Store at 2° to 30°C (b) (4)
   (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 single-use vials 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** (Section 2.3.P.1, Vol. 1.4 and pages 4007):
6. Container/Closure:

| Drug content/vial | (b) (4) |
|---|---|
| 10 mg Base | |
| 20 mg Base | |

7. All manufacturing will be done by: (b) (4)

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Date of Review: 9/27/06 Date of Submission: 8/18/06

Primary Reviewer: Jim Barlow Date: 9/28/06

Team Leader: John Grace Date: John J Grace 9-28-2006

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cc:

ANDA: 77-826
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\SICOR\LTRS&REV\77826na3_labelingreview.doc
Review

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

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ANDA Number: 77-826
Date of Submission: May 12, 2006
Applicant's Name: SICOR Pharmaceuticals, Inc.
Established Name: Fenoldopam Mesylate Injection USP, 10 mg/mL

---

**Labeling Deficiencies:**

1. **CONTAINER – 1 mL and 2 mL single-dose vials**
   Satisfactory in **final print** as of the May 12, 2006 electronic submission
   \\CDSESUB1\N77826\N_000\2006-05-12\SICOR Fenoldopam Mesylate Injection, USP 8211-01 vial.pdf

   \\CDSESUB1\N77826\N_000\2006-05-12\SICOR Fenoldopam Mesylate Injection, USP 8221-01 vial.pdf

2. **CARTON – 1 mL and 2 mL single-dose**
   Satisfactory in **final print** as of the May 12, 2006 electronic submission
   \\CDSESUB1\N77826\N_000\2006-05-12\SICOR Fenoldopam Mesylate Injection, USP 8211-01 carton.pdf

   \\CDSESUB1\N77826\N_000\2006-05-12\SICOR Fenoldopam Mesylate Injection, USP 8221-01 carton.pdf

3. **PACKAGE INSERT**
   Please revise your labeling to be in accord with the enclosed, most recently approved package insert labeling for generic fenoldpam mesylate injection, USP. This generic labeling includes the necessary **Best Pharmaceuticals** for **Children Act** language associated with pediatric exclusivity. This labeling was based on the most recently approved package insert labeling for the reference listed drug, Corlopam® (NDA 19-922/S-005; approved April 1, 2004).

Please revise your labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2alG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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

Enclosed: A copy of the most recently approved package insert labeling for generic fenoldpam mesylate injection, USP. This labeling was based on the most recently approved package insert labeling for the reference listed drug, Corlopam® (NDA 19-922/S-005; approved April 1, 2004).

**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 April 1, 2004 for the RLD. Used recently approved insert and container/carton labeling for ANDA 77-155 (fenoldopam injection) produced by Sandoz for guidance.
2. **Patent/ Exclusivities:**

**Patent Data – NDA 19-922**

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| | | 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 |
|---|---|---|---|
| I-422 | INDICATED FOR THE IN-HOSPITAL SHORT-TERM (UP TO 4 HOURS) REDUCTION IN BLOOD PRESSURE IN PEDIATRIC PATIENTS | 4/1/07 | Carved Out and substituted with Pediatric Division/New Drug Division and OGD recommended statements |

3. Storage/Dispensing Conditions:
   NDA: Store at 2° to 30°C.
   ANDA: Store at 2° to 30°C [redacted] (b) (4)
   (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 single-use vials 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** (Section 2.3.P.1, Vol. 1.4 and pages 4007):
6. Container/Closure:

| Drug content/vial | [redacted] (b) (4) |
|---|---|
| 10 mg Base | |
| 20 mg Base | |

7. All manufacturing will be done by: [redacted] (b) (4)

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Date of Review: 5/24/06 Date of Submission: 5/12/06

Primary Reviewer: Jim Barlow Date: 5/24/06

Team Leader: John Grace Date:

John J Grace 6.30.06

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cc:

ANDA: 77-826
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\SICOR\LTRS&REV\77826na2.l.doc
Review

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

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ANDA Number: 77-826 Date of Submission: July 29, 2005
Applicant's Name: SICOR Pharmaceuticals, Inc.
Established Name: Fenoldopam Mesylate Injection USP, 10 mg/mL

---

**Labeling Deficiencies:**

1. **CONTAINER – 1 mL single-dose vials**

Revise your container labels accordingly –

NDC # 1 mL Single Use Vial
**Fenoldopam**
**Mesylate**
**Injection, USP**
**10 mg/mL**
**DILUTE PRIOR TO**
**IV INFUSION**
**Sterile**
**Rx only**
**Mfd: Sicor .....**

2. **CONTAINER – 2 mL single-dose vials**

Revise your container labels accordingly and utilize different contrasting/colors and/or boxing. Your carton is very difficult to read -

NDC # 2 mL Single Use Vial
**Fenoldopam**
**Mesylate**
**Injection, USP**
**20 mg/2 mL (10mg/mL)**
**DILUTE PRIOR TO**
**IV INFUSION**
**Sterile**
**Rx only**
**Mfd: Sicor .....**

3. **CARTON – 1 mL single-dose**

Revise your carton labels accordingly-

NDC #

**Fenoldopam**
**Mesylate**
**Injection, USP**
**10 mg/mL**

**DILUTE PRIOR TO IV INFUSION**
**Sterile**
**1 mL Single Use Vial**
**Rx only**

**Mfd: Sicor .....**

4. **CARTON – 2 mL single-dose**

Revise your carton labels accordingly and utilize different contrasting/colors and/or boxing. Your carton is very difficult to read -

NDC #

**Fenoldopam**
**Mesylate**
**Injection, USP**
**20 mg/2 mL**
**(10 mg/mL)**

**DILUTE PRIOR TO IV INFUSION**
**Sterile**
**2 mL Single Use Vial**
**Rx only**

**Mfd: Sicor .....**

5. **PACKAGE INSERT**

Please revise your labeling to be in accord with the enclosed mocked-up copy of fenoldopam package insert labeling.

Please revise your labeling as described above and submit electronically. The immediate container labels and carton labeling may be submitted either electronically or in hard copy.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2alG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

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

Enclosed: A copy of mocked-up package insert labeling for fenoldopam injection.

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

# CHEMISTRY REVIEWS

# ANDA 77-826

## Fenoldopam Mesylate Injection USP, 10 mg /mL, packaged in 1mL and 2 mL vials

## Sicor Pharmaceuticals, Inc.

**Yusuf Amin**
**Chemistry Division I**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA # 77-826

2. REVIEW #: 2

3. REVIEW DATE: 08/15/2006

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 29-JUL-2005 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | 20-JUL-2006 |
| Amendment Labeling | 18-AUG-2006 |
| Amendment Micro | 31-AUG-2006 |
| Amendment Labeling | 29-SEP-2006 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Sicor Pharmaceuticals, Inc. |
| Address: | 19 Hughes<br>Irvine, CA 92618-1902 |
| Attention: | Sonia Hernandez |
| Telephone:<br>Fax: | (949) 455-4779<br>(949) 583-7351 |

8. DRUG PRODUCT NAME/CODE/TYPE:

Fenoldopam Mesylate Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

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 Hospira. Sicor 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 Hospira.

Sicor certifies that in its opinion and to the best of its knowledge, the pediatric exclusivity code No. I-422 expiring on April 1st 2007 will not be infringed, Sicor does not intend to market this product with the aforementioned exclusivities prior to the expiration date.

10. PHARMACOL. CATEGORY: Short-term management of severe hypertension.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg /mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

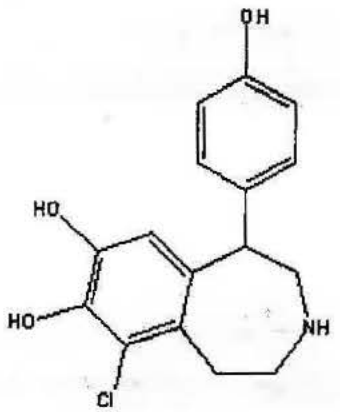
_____SPOTS product – Form Completed

__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:




$CH_3SO_3H$

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | | | | | |
| (b) (4) | III | (b) (4) | | 4 | | | |
| | III | | | 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:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| Corlopam® Hospira | 19-922 | RLD |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | Acceptable | 14-SEP-2006 | P. Dexter |
| EES | Pending | | |
| Methods Validation | N/A | | |
| Labeling | Acceptable | 5-OCT-2006 | J. Barlow |
| Bioequivalence | Acceptable | 06-JAN-2006 | B. Fritsch |
| EA | N/A | | |
| 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 77-826

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

CMC, Bio, Micro, and labeling are acceptable; EER is pending.

### 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). It is 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 Hospira. 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.

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

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

### C. Basis for Approvability or Not-Approval Recommendation

CMC, Bio, Micro, and labeling are acceptable; EER is pending.



Following this page, 16 Pages Withheld in Full as (b)(4)

(b) (4)

30. **MICROBIOLOGY: Acceptable, P. Dexter, 14-SEP-2006**

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS:**
The drug substance and the drug product are compendium items, therefore methods validation is not required.

32. **LABELING: Acceptable, J. Barlow, 5-OCT-2006,**

33. **ESTABLISHMENT INSPECTION: Pending**

34. **BIOEQUIVALENCE: Acceptable 06-JAN-2006, B. Fritsch**

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory in review 1**
Sicor requests a categorical exclusion from requirement of an environmental assessment statement and certifies compliance of all applicable local, state, and federal environmental regulations (p. 1018).

cc: ANDA # 77-826
ANDA DUP # 77-826
DIV FILE
Field Copy

Endorsements:

Reviewer:HFD-623/Y.Amin/11.15.06
Team Leader:HFD-623/A. Mueller/
Project Manager: HFD-617/S. Eng/

11/21/06
11-15-06
11/15/06

C. CC Block: N/A

F/T: se

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**TYPE OF LETTER: CMC APPROVABLE**

# ANDA 77-826

## Fenoldopam Mesylate Injection USP, 10mg (base)/mL, 1mL and 2 mL vials

## Sicor Pharmaceuticals, Inc.

**Yusuf Amin**
**Chemistry Division I**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA # 77-826

2. REVIEW #: 1

3. REVIEW DATE: 11/18/2005

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| None | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 29-JUL-2005 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Sicor Pharmaceuticals, Inc. |
| Address: | 19 Hughes<br>Irvine, CA 92618-1902 |
| Attention: | Rosalie A. Lowe |
| Telephone:<br>Fax: | (949) 457-2808<br>(949) 583-7351 |

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

9. LEGAL BASIS FOR SUBMISSION:
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 Hospira. Sicor 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 Hospira.

Sicor certifies that in its opinion and to the best of its knowledge, the pediatric exclusivity code No. I-422 expiring on April 1st 2007 will not be infringed, Sicor does not intend to market this product with the aforementioned exclusivities prior to the expiration date.

10. PHARMACOL. CATEGORY: Short-term management of severe 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):

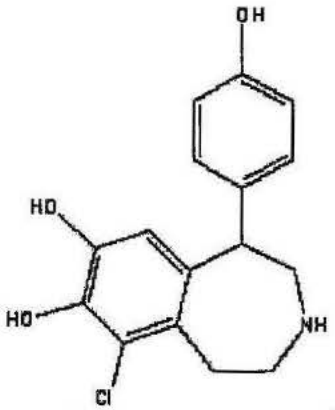
_____SPOTS product – Form Completed

_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:




$CH_3SO_3H$

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | | | | | |
| (b) (4) | III | (b) (4) | | 4 | | | |
| | III | | | 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:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| Corlopam® Hospira | 19-922 | RLD |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | Pending | | |
| EES | Pending | | |
| Methods Validation | N/A | | |
| Labeling | Pending | | |
| Bioequivalence | Pending | | |
| EA | N/A | | |
| 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 77-826

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The CMC section is deficient 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). It is 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 Hospira. 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.

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

The recommended dose 0.1μg/kg/min is administered by continuous intravenous injection with increments of 0.05μg/kg/min to 0.1μg/kg/min 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 is deficient.
- 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

Yusuf Amin

B. Endorsement Block

Reviewer:HFD-623/Y.Amin/11/30/2005 12/14/05
Team Leader:HFD-623/A. Mueller/12/12/05 A Mueller 12-14-05
Project Manager: HFD-617/S. Eng/12/13/05

f/t:ard/12/13/05

C. CC Block: N/A

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(b) (4)

[redacted]

**30. MICROBIOLOGY: Pending**

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

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

The drug substance and the drug product are compendium items, therefore methods validation is not required.

**32. LABELING: Pending**

**33. ESTABLISHMENT INSPECTION: Pending**

**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**

Sicor requests a categorical exclusion from requirement of an environmental assessment statement and certifies compliance of all applicable local, state, and federal environmental regulations (p. 1018).

## 36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #77-826 APPLICANT: Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Fenoldopam Mesylate Injection USP, 10 mg (Base)/mL, 1 mL and 2 mL Vials

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.


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 is under review . The deficiencies found will be 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 a separate cover.

5. (b) (4)

Sincerely yours,

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

cc: ANDA # 77-826
ANDA DUP # 77-826
DIV FILE
Field Copy

Endorsements:

Reviewer:HFD-623/Y.Amin/11/30/2005 12/14/05
Team Leader:HFD-623/A. Mueller/12/12/05 a/mueller 12-14-05
Project Manager: HFD-617/S. Eng/12/13/05 12/14/05

C. CC Block: N/A

F/T:ard/12/13/05

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**TYPE OF LETTER: NOT APPROVABLE - MINOR**

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

# MICROBIOLOGY REVIEWS

# Product Quality Microbiology Review
## Review for HFD-620

**12/September/2006**

**ANDA:** 77-826

**Drug Product Name**
**Proprietary:** NA
**Non-proprietary: Fenoldopam Mesylate Injection**
**Drug Product Priority Classification:** NA

**Review Number:** #2

**Dates of Submission(s) Covered by this Review**

| Letter | Stamp | Consult Sent | Assigned to Reviewer |
|---|---|---|---|
| 8/31/2005 | 9/01/2005 | NA | 09/06/2006 |

**Submission History (for amendments only)**

| Submission Date(s) | Microbiology Review # | Review Date(s) |
|---|---|---|
| 07/29/2005 | 1 | 07/06/2006 |

**Applicant/Sponsor**
**Name:** SICOR Pharmaceuticals, Inc.
**Address:** 19 Hughes
Irvine, CA 92618-1902
**Representative:** Sonia Hernandez
**Telephone:** (949) 455-4779

**Name of Reviewer:** Paul L. Dexter

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

# Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** ANDA Amendment

2. **SUBMISSION PROVIDES FOR:** Response to Agency's deficiency letter.

3. **MANUFACTURING SITE:** [redacted] (b) (4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Injectable, Intravenous, 10 mg Base/ml supplied as 10 mg Base/1 ml single dose vial and 20 mg Base/2 ml single dose vial.

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

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the in-hospital, short term (up to 48 hours) management of severe hypertension.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:** None.

**filename:** V:\MICROREV\77-826a1.doc

# Executive Summary

## I. Recommendations

**A. Recommendation on Approvability -**
The submission is **recommended** for approval on the basis of sterility assurance.

**B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -** NA

## II. Summary of Microbiology Assessments

**A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** (b) (4) (b) (4)

**B. Brief Description of Microbiology Deficiencies** – N/A

**C. Assessment of Risk Due to Microbiology Deficiencies -**
No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

## III. Administrative

**A. Reviewer's Signature** _____

**B. Endorsement Block**
Microbiologist / Paul L. Dexter
Microbiology Supervisor / Neal J. Sweeney, Ph.D.

**C. CC Block**
cc:
Original ANDA
Division File
Field Copy

Neal J. Sweeney
9-14-06



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# Product Quality Microbiology Review
## Review for HFD-620

06 /July/2006

**ANDA:** 77-826

**Drug Product Name**
**Proprietary:** NA
**Non-proprietary: Fenoldopam Mesylate Injection**
**Drug Product Priority Classification:** NA

**Review Number:** #1

**Dates of Submission(s) Covered by this Review**

| Letter | Stamp | Consult Sent | Assigned to Reviewer |
|---|---|---|---|
| July 29, 2005 | Aug 1, 2005 | NA | June 20, 2006 |

**Submission History (for amendments only)**

| Submission Date(s) | Microbiology Review # | Review Date(s) |
|---|---|---|
| NA | NA | NA |

**Applicant/Sponsor**
**Name:** SICOR Pharmaceuticals, Inc.
**Address:** 19 Hughes
Irvine, CA 92618-1902
**Representative:** Rosalie A. Lowe
**Telephone:** (949) 457-2808

**Name of Reviewer:** Paul L. Dexter

**Conclusion:** This submission is **not recommended** for approval on the basis of sterility assurance.

# Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original ANDA

2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product.

3. **MANUFACTURING SITE:** [redacted] (b) (4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Injectable, Intravenous, 10 mg Base/ml supplied as 10 mg Base/1 ml single dose vial and 20 mg Base/2 ml single dose vial.

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

6. **PHARMACOLOGICAL CATEGORY:** Indicated for the in-hospital, short term (up to 48 hours) management of severe hypertension.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:** None.

**filename:** V:\MICROREV\77-826.doc

# Executive Summary

## I. Recommendations

**A. Recommendation on Approvability -**
The submission is not recommended for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "H. List of Microbiology Deficiencies and Comments" sections.

**B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -** NA

## II. Summary of Microbiology Assessments

**A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** (b) (4) (b) (4)

**B. Brief Description of Microbiology Deficiencies –** (b) (4) (b) (4)

**C. Assessment of Risk Due to Microbiology Deficiencies -**
The safety risk associated with the microbiology deficiencies is considered moderate.

## III. Administrative

**A. Reviewer's Signature**

**B. Endorsement Block**
Microbiologist / Paul L. Dexter
Microbiology Supervisor / Neal J. Sweeney, Ph.D.

**C. CC Block**
cc:
Original ANDA
Division File
Field Copy

8-28-06



Following this page, 16 Pages Withheld in Full as (b)(4)

## 3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 77-826 APPLICANT: SICOR Pharmaceuticals, Inc.

DRUG PRODUCT: Fenoldopam Mesylate

A. Microbiology Deficiencies:

1. (b) (4)

2.

3.

4.

B. Comments:

1. [redacted] (b) (4)

Please clearly identify your amendment to this facsimile as RESPONSE TO MICROBIOLOGY DEFICIENCIES. The RESPONSE TO MICROBIOLOGY DEFICIENCIES should also be noted in your cover page/letter.

Sincerely yours,

Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

# BIOEQUIVALENCE REVIEWS

# OFFICE OF GENERIC DRUGS
# DIVISION OF BIOEQUIVALENCE

ANDA #: 77-826 SPONSOR: Sicor Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM: Fenoldopam Mesylate Injection USP

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

STUDY SUMMARY: The test drug product is a parental solution intended solely for administration by injection and contains the same active an inactive ingredients in the same concentration as the approved reference listed product. A waiver of the in-vivo bioavailability/bioequivalence study requirements is granted [21 CFR 320.22(b)(1)]

**DSI INSPECTION STATUS**

| Inspection needed: No | Inspection status: | Inspection results: |
|---|---|---|
| First Generic _No__<br>New facility _____<br>For cause ____<br>Other ____ | Inspection requested: (date)<br>Inspection completed: (date) | |

PROJECT MANAGER: Beth Fabian Fritsch, R.Ph., MBA BRANCH: IV

INITIAL: _____ DATE: 1/3/06

TEAM LEADER: Aida Lizzie Sanchez, Pharm.D. BRANCH: IV

INITIAL: _____ DATE: 1/4/06

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

INITIAL: _____ DATE: 1/6/06

## DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.:** | 77-826 |
| **Drug Product Name** | Fenoldopam Mesylate Injection USP |
| **Strength** | 10 mg/mL, 1 mL and 2 mL Vials |
| **Applicant Name** | Sicor Pharmaceuticals, Inc. |
| **Address** | 19 Hughes<br>Irvine, CA 92618-1902 |
| **Submission Date(s)** | July 29, 2005 |
| **Amendment Date(s)** | NA |
| **Reviewer** | Beth Fabian Fritsch, R.Ph., MBA |
| **First Generic** | No |
| **File Location** | V: firmsnz/sicor/ltrs&rev/77826W0705.doc |

### I. Submission Summary

The test product is qualitatively and quantitatively the same as the reference listed drug. Therefore, Sicor Pharmaceuticals, Inc.'s Fenoldopam Mesylate Injection USP, 10 mg/mL, 1 mL and 2 mL vials is deemed bioequivalent to the reference listed drug Corlopam® Injection (Fenoldopam Mesylate Injection USP),10 mg/mL under 21 CFR 320.22(b)(1).

#### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Fenoldopam Mesylate Injection USP, 10 mg/mL |
| **Reference Product** | Corlopam Injection, 10 mg/mL |
| **RLD Manufacturer** | Hospira |
| **NDA No.** | 19-922 |
| **RLD Approval Date** | September 23, 1997 |
| **Indication** | **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** |

#### B. Formulation

| Ingredient | Test | Reference |
|---|---|---|
| Fenoldopam Mesylate | 10 mg/mL | 10 mg/mL |
| Citric Acid Anhydrous, USP | 3.44 mg | 3.44 mg |
| Propylene Glycol, USP | 518 mg | 518 mg |
| Sodium Citrate Dihydrate, USP | 0.61 mg | 0.61 mg |
| Sodium Metabisulfite, NF | 1 mg | 1 mg |
| Water for Injection, USP | q.s. 1 mL | (b) (4) |

**Recommendations**

The Division of Bioequivalence agrees that the information submitted by Sicor Pharmaceuticals, Inc. demonstrates that its test product Fenoldopam Mesylate Injection USP, 10 mg/mL, 1 mL and 2 mL Vials falls under the criteria set forth in 21 CFR 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waiver is granted.

Beth Fabian Fritsch, R.Ph., MBA
Project Manager, Branch IV

A. L. Sanchez, Pharm. D. 1/4/06

Aida Lizzie Sanchez, Pharm.D.
Special Assistant to the Director
Division of Bioequivalence

Dale P. Conner 1/6/06

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-826 APPLICANT: Sicor Pharmaceuticals, Inc.

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

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

Please note that the bioequivalence 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 bioequivalence 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 77-826
ANDA DUPLICATE
DIVISION FILE

Printed in final on

Endorsements: (Final with Dates)
HFD-655/ B. Fritsch 1/3/06
HFD-655/ L. Sanchez 1/4/06
HFD-650/ D. Conner 1/6/06

BIOEQUIVALENCE - ACCEPTABLE Submission date: July 29, 2005

1. **WAIVER** (WAI)

Strengths: 10 mg/mL,
1 ml and 2 mL
**Outcome:AC**

**Outcome: AC- Acceptable**

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# ANDA 77826

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

**OGD APPROVAL ROUTING SUMMARY**

ANDA # 77-826 Applicant Sicor Pharmaceuticals, Inc.

Drug Fenoldopam Mesylate INJ, USP Strength(s) 10mg Base/mL

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

| REVIEWER: | DRAFT Package | FINAL Package |
|---|---|---|
| 1. Martin Shimer<br>Chief, Reg. Support Branch | Date 21 Sept 06<br>Initials SEP | Date 3/7/07<br>Initials Rw for |

Contains GDEA certification: (Yes) No (required if sub after 6/1/92)

Determ. of Involvement? Yes (No)

Pediatric Exclusivity System

RLD = NDA# 19922

Patent/Exclusivity Certification (Yes) No

Date Checked N/A

If Para. IV Certification- did applicant

Nothing Submitted

Notify patent holder/NDA holder Yes No

Written request issued

Was applicant sued w/in 45 days: Yes No

Study Submitted

Has case been settled: Yes No

Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes No

Date of latest Labeling Review/Approval Summary 6/30/06 carried out I-422.

Any filing status changes requiring addition Labeling Review Yes No

Type of Letter: - No relevant patents

Comments: - Exc. I-422 carried out so can go to market before 4/1/07

| | | |
|---|---|---|
| 2. Project Manager, Sims Team 1<br>Review Support Branch | Date 9/18/06<br>Initials R | Date<br>Initials |

Original Rec'd date 7/29/05

Date Acceptable for Filing 8/1/05 ✓

Patent Certification (type) I

Date Patent/Exclus.expires N/A

Citizens' Petition/Legal Case Yes (No)

(If YES, attach email from PM to CP coord)

First Generic 76656 Ap'd Yes (No)

Priority Approval on 12/1/03 Yes (No)

(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

Acceptable Bio reviews tabbed (Yes) No

Suitability ~~Petition~~/Pediatric Waiver

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date

Previously reviewed and CGMP def. /NA Minor issued Date

EER Status (Pending) Acceptable OAI

Date of EER Status

Date of Office Bio Review 1/6/06

Date of Labeling Approv. Sum 10/5/06

Labeling Acceptable Email Rec'd Yes No

Labeling Acceptable Email filed Yes No

Date of Sterility Assur. App. 9/14/06

Methods Val. Samples Pending Yes No

MV Commitment Rcd. from Firm Yes No

Modified-release dosage form: Yes No

Interim Dissol. Specs in AP Ltr: Yes

Comments:

| | | |
|---|---|---|
| 3. David Read **(PP IVs Only)** Pre-MMA Language included<br>OGD Regulatory Counsel, Post-MMA Language Included<br>Comments: N/A. No listed patents in the 'Orange Book'. | | Date 3/1/07<br>Initials Rw for |

| | | |
|---|---|---|
| 4. Div. Dir./~~Deputy Dir.~~<br>Chemistry Div. I ~~II OR III~~<br>Comments: AP pending EER clearance | | Date 11/29/06<br>Initials RK |

DAC

1. ✓ 2. ✓ 3. ✓ 4. ✓ 5. ✓ 6. ✓

**REVIEWER:** **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
NTA. Multiple ANDAs have been approved for this drug product. (Pharmaforce, Bedford, Sandoz).
RLD = Carlopam Injection 10mg(base)/mL Hospira Inc. NDA 19-922, (001)

6. Vacant Date_____
Deputy Dir., DLBS Initials_____

7. Peter Rickman Date 3/7/07
Director, DLPS Initials Request for
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments Bioequivalence waiver granted under 21 CFR 320.22(b)(1) drug product is "AB" to the RLD. Office-level biopr endorsed 1/6/06. FBL found acceptable for approval 10/5/06. Microbiology/Sterility review found acceptable 9/14/06. CMC found acceptable for approval 11/15/06.

8. Robert L. West Date 3/7/2007 Just
Deputy Director, OGD Initials Request for
Para.IV Patent Cert: Yes (No); Pending Legal Action: Yes (No); Petition: Yes (No)
Press Release Acceptable
Comments: Acceptable LER dated 3/6/07 (verified 3/7/07). No OPE issues noted. There are no unexpired patents listed in the current "Orange Book" for this drug product. The I-422 exclusivity has been carved-out of Sicor's labeling and replaced with statements found acceptable to the PEDS team and review division. This exclusivity will expire on 4/1/07.
This ANDA is recommended for approval.

9. Gary Buehler Date 3/7/07
Director, OGD Initials Rec'd for
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue
Press Release Acceptable

10. Project Manager, Team Simon Date 3/7/07
Review Support Branch Initials
_____Date PETS checked for first generic drug (just prior to notification to Firm)
Applicant notification:
10:30A Time notified of approval by phone 10:30AM Time approval letter faxed
FDA Notification:
3/7/07 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/7/07 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou11.doc (08/25/2006)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

---

Simon Eng

3/7/2007 10:55:42 AM

## Eng, Simon

**From:** Grace, John F
**Sent:** Wednesday, November 29, 2006 1:29 PM
Barlow, James T; Eng, Simon
**Subject:** RE: 77826/SICOR/Fenoldopam Mesylate Inj USP, 10 mg/mL

77-826/SICOR

concur

-----Original Message-----
From: Barlow, James T
Sent: Wednesday, November 29, 2006 1:28 PM
To: Eng, Simon; Grace, John F
Subject: RE: 77826/SICOR/Fenoldopam Mesylate Inj USP, 10 mg/mL

I checked Drugs@FDA,OB and USP.
The labeling Approval Summary signed by John Grace on 10/5/06 remains acceptable.

-----Original Message-----
From: Eng, Simon
Sent: Tuesday, November 28, 2006 7:41 AM
To: Barlow, James T; Grace, John F
Subject: 77826/SICOR/Fenoldopam Mesylate Inj USP, 10 mg/mL

Hi Jim and John,
Please conduct a leabling approval sign-off review.
Thanks,

labeling

mon

Simon Eng
Project Manager, OGD, FDA
7500 Standish Place, MPN-II, HFD-617
Rockville, MD 20855
Phone # 301-827-5765
Fax # 301-594-0180
Email Address: simon.eng@fda.hhs.gov

DEC 16 2005

## 36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #77-826 APPLICANT: Sicor Pharmaceuticals, Inc.

DRUG PRODUCT: Fenoldopam Mesylate Injection USP, 10 mg (Base)/mL, 1 mL and 2 mL Vials

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

(b) (4)

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 is under review . The deficiencies found will be 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 a separate cover.

5. [redacted] (b) (4)

Sincerely yours,

Rashmikant M. 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 Nbr: 77-826** **FIRM NAME**: SICOR PHARMACEUTICALS, INC.

**RELATED APPLICATION(S):** NA

**First Generic Product Received? NO**

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

| **Bio Assignments:** | | ☒ **Micro Review** |
|---|---|---|
| ☒ **BPH** | ☐ **BCE** | |
| ☐ **BST** | ☐ **BDI** | |

**Random Queue: 1**
Chem Team Leader: Bykadi, Raj PM: Simon Eng Labeling Reviewer: James Barlow

| | |
|---|---|
| **Letter Date**: JULY 29, 2005 | **Received Date**: AUGUST 01, 2005 |
| **Comments: EC- 1 YES** **On Cards:** YES<br>**Therapeutic Code:** 1020100 ANTI- HYPERTENSIVE AGENTS | |
| **Archival Format:** PAPER **Sections** I **(356H Sections per EDR Email)**<br>**Review copy**: YES E-Media Disposition: YES SENT TO EDR<br>Not applicable to electronic sections<br>Field Copy Certification (Original Signature) YES | |
| **Methods Validation Package** (3 copies PAPER archive) **YES**<br>(Required for Non-USP drugs) | |
| **Cover Letter** YES | **Table of Contents** YES |
| PART 3 Combination Product Category N Not a Part3 Combo Product<br>(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm | |

| | |
|---|---|
| **Reviewing CSO/CST** **Stanley Shepperson** Stanley Shepperson 9/26/05<br>**Date 26-Sep-05** | **Recommendation:**<br>☒ **FILE** ☐ **REFUSE to RECEIVE** |
| **Supervisory Concurrence/Date:** Martin Shimer Sandra J. Middleton for Date: 9/29/05 | |
| **ADDITIONAL COMMENTS REGARDING THE ANDA:** | |
| **Top 200 Drug Product:** | |

ACCEPTABLE

| | | |
|---|---|---|
| Sec. I | **Signed and Completed Application Form (356h)** YES<br>(Statement regarding Rx/OTC Status) RX YES | ☒ |
| Sec. II | **Basis for Submission** **NDA# : 19-922**<br>Ref Listed Drug: CORLOPAM Firm: HOSPIRA INC.<br>ANDA suitability petition required? NO<br>If Yes, then is change subject to PREA (change in dosage form, route, active ingredient)<br>For products subject to PREA a wavier request must be granted prior to approval of ANDA.<br>Wavier Granted: | ☒ |
| Sec. III | **Patent Certification**<br>1. Paragraph: I<br>2. Expiration of Patent: NA<br>A. Pediatric Exclusivity Submitted?<br>B. Pediatric Exclusivity Tracking System checked?<br>**Exclusivity Statement:** YES | ☒ |
| Sec. IV | **Comparison between Generic Drug and RLD-505(j)(2)(A)**<br>1. Conditions of use SAME<br>2. Active ingredients SAME<br>3. Route of administration SAME<br>4. Dosage Form SAME<br>5. Strength SAME | ☒ |
| Sec. V | **Labeling** (Mult Copies N/A for E-Submissions) **HOW SUPPLIED:**<br>Single-use vials: 10 mg/1 mL and 20 mg/2 mL<br>1. 4 copies of draft (each strength and container) or 12 copies of FPL YES<br>2. 1 RLD label and 1 RLD container label YES<br>3. 1 side by side labeling comparison with all differences annotated and explained YES<br>4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.) | ☒ |
| Sec. VI | **Bioavailability/Bioequivalence**<br>**1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NO<br>**2. Request for Waiver of In-Vivo Study(ies): YES**<br>**3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) yes<br>**4. Lot Numbers of Products used in BE Study(ies):** n/a<br>**5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below) | ☒ |
| Study Type | **IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA<br>a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC)<br>b. EDR Email: Data Files Submitted: YES SENT TO EDR<br>c. In-Vitro Dissolution: NO | ☒ |

| | | |
|---|---|---|
| Study Type | **IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO<br>a. Properly defined BE endpoints (eval. by Clinical Team)<br>b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120)<br>c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team)<br>d. EDR Email: Data Files Submitted | ☐ |
| Study Type | **TRANSDERMAL DELIVERY SYSTEMS** NO<br>a. In-Vivo PK Study<br>1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC)<br>2. In-Vitro Dissolution<br>3. EDR Email: Data Files Submitted<br>b. Adhesion Study<br>c. Skin Irritation/Sensitization Study | ☐ |
| Study Type | **NASALLY ADMINISTERED DRUG PRODUCTS** NO<br>a. Solutions (Q1/Q2 sameness):<br>1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)<br>b. Suspensions (Q1/Q2 sameness):<br>1. In-Vivo PK Study<br>a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC)<br>b. EDR Email: Data Files Submitted<br>2. In-Vivo BE Study with Clinical EndPoints<br>a. Properly defined BE endpoints (eval. by Clinical Team)<br>b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120)<br>c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team)<br>d. EDR Email: Data Files Submitted<br>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)** NO<br>a. Pilot Study (determination of ED50)<br>b. Pivotal Study (study meets BE criteria 90%CI or 80-125) | ☐ |
| **Sec. VII** | **Components and Composition Statements**<br>1. Unit composition and batch formulation Yes.<br>2. Inactive ingredients as appropriate Yes. Q1/Q2 | ☒ |

| | | |
|---|---|---|
| **Sec. VIII** | **Raw Materials Controls**<br>1. **Active Ingredients**<br>a. Addresses of bulk manufacturers YES<br>b. Type II DMF authorization letters or synthesis YES- DMF (b) (4)<br>c. COA(s) specifications and test results from drug substance mfgr(s) YES<br>d. Applicant certificate of analysis YES<br>e. Testing specifications and data from drug product manufacturer(s) YES<br>f. Spectra and chromatograms for reference standards and test samples YES<br>g. CFN numbers<br>2. **Inactive Ingredients**<br>a. Source of inactive ingredients identified YES<br>b. Testing specifications (including identification and characterization) YES<br>c. Suppliers' COA (specifications and test results) YES<br>d. Applicant certificate of analysis YES | ☒ |
| **Sec.IX** | **Description of Manufacturing Facility**<br>1. Full Address(es)of the Facility(ies) YES<br>2. CGMP Certification: YES<br>3. CFN numbers YES | ☒ |
| **Sec. X** | **Outside Firms Including Contract Testing Laboratories** ***(NO OUTSIDE FIRMS USED)***<br>1. Full Address<br>2. Functions<br>3. CGMP Certification/GLP<br>4. CFN numbers | ☒ |
| **Sec. XI** | **Manufacturing and Processing Instructions**<br>1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES<br>2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES<br>3.If sterile product: (b) (4) YES<br>4.Filter validation (b) (4) YES<br>5. Reprocessing Statement YES<br>**Intended Commercial Batch Size:**<br>(b) (4) | ☒ |
| **Sec. XII** | **In-Process Controls**<br>1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation YES<br>2. In-process Controls - Specifications and data YES<br>(b) (4) | ☒ |

| | | |
|---|---|---|
| Sec. XIII | **Container**<br>1. Summary of Container/Closure System (if new resin, provide data) YES<br>2. Components Specification and Test Data (Type III DMF References) YES<br>3. Packaging Configuration and Sizes YES<br>4. Container/Closure Testing YES<br>5. Source of supply and suppliers address YES | ☒ |
| Sec. XIV | **Controls for the Finished Dosage Form**<br>1. Testing Specifications and Data YES<br>2. Certificate of Analysis for Finished Dosage Form YES | ☒ |
| Sec. XV | **Stability of Finished Dosage Form**<br>1. Protocol submitted YES<br>2. Post Approval Commitments YES<br>3. Expiration Dating Period YES- (b) (4)<br>4. Stability Data Submitted YES<br>a. 3 month accelerated stability data YES<br>b. Batch numbers on stability records the same as the test batch YES | ☒ |
| Sec. XVI | **Samples** - Statement of Availability and Identification of:<br>1. Drug Substance YES<br>2. Finished Dosage Form YES<br>3. Same lot numbers YES | ☒ |
| Sec. XVII | **Environmental Impact Analysis Statement** YES | ☒ |
| Sec. XVIII | **GDEA (Generic Drug Enforcement Act)/Other:**<br>1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])<br>2. Debarment Certification (original signature): YES<br>3. List of Convictions statement (original signature) YES | ☒ |

**OGD Template Revised 04/01/2004 /T.Hinchliffe**

# ANDA 77-846 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

___ 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD.

___ 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. 19-922 (CoRlopam) PI

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

___ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ✓ yes ___ no)

✓ 19) Final Grammar review on letter.

___ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

___ 22) Document in record book.

Signature _____ date _____

ANDA 77-826

SEP 29 2005

Sicor Pharmaceuticals, Inc.
Attention: Rosalie A. Lowe
19 Hughes
Irvine, CA 92618-1902

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/mL, 1 mL and 2 mL vials

DATE OF APPLICATION: July 29, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 1, 2005

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:

Simon Eng
Project Manager
301-827-5765

Sincerely yours,

for

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

ANDA 77-826

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/
HFD-143/OIM/DRM

Endorsement:
HFD-615/M.Shimer, Chief, RSB S. Middleton date 9/29/05
HFD-615/S.Shepperson, CSO /s/ Per. S.Shepperson date 9/29/05

Word File V:\CDSNAS\OGDS11\FIRMSNZ\SICOR\LTRS&REV\77826.ACK.DOC

F/T SS 9/29/05

ANDA Acknowledgment Letter!

## Howard, Eda

**From:** EDRAdmin@cder.fda.gov
**Sent:** Wednesday, August 10, 2005 3:35 PM
**To:** Howarde@cder.fda.gov; washingtone@cder.fda.gov; FARAHIFARD@cder.fda.gov; GREENW@cder.fda.gov; NGUYENH@cder.fda.gov; SAUNDERSJA@CDER.FDA.GOV
**Cc:** schumaker@cder.fda.gov; esub@cder.fda.gov; talastash@cder.fda.gov; emmonsp@cder.fda.gov; langhnojau@cder.fda.gov; Tokoli@cder.fda.gov; EDRAdmin@cder.fda.gov
**Subject:** EDR - ANDA 077826 from SICOR PHARMS drug name FENOLDOPAM MESYLATE

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-600:

ANDA # N77826
Incoming Document Type: N
Incoming Document Type Sequence Number: 000
Supplement Modification Type:
Letter Date: 7/29/2005

It has sections 1, 2.
The network path location is: \\CDSESUBOGD1\N77826\N_000\2005-07-29
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAdmin@cder.fda.gov

Thanks,
Prentiss

## Woodard-Farmer, Felicia *

**To:** Talastas, Hercules*; Emmons, Prentiss*
**Cc:** EDRAdmin@cder.fda.gov; CDER-DDR600; Howard, Eda; Washington, Edward; Langhnoja, Urvi *
**Subject:** OGD Electronic Submissions -- ANDA: 77-826, Letter Date: 29 July 2005 - Submission Type: NEW NDOC - MIXED electronic

DDR 600 has received the following electronic submission and entered the following code and volume number in COMIS and ECH. We will scan and forward the XVOLUME(S) out to EDR. The XVOLUME will be sent on the next courier run.

1) ANDA: 77-826

2) Letter Date: 29 July 2005

3) Stamp Date: 01 August 2005

4) Document Code: N-000

5) Division: 600

6) This submission contains:

| | | | | |
|---|---|---|---|---|
| CD-ROMs | 1 | Original(s) | 0 | Duplicate(s)* |
| Diskettes | 0 | Original(s) | 0 | Duplicate(s) |
| Tapes | 0 | Original(s) | 0 | Duplicate(s) |
| DVD-ROMs | 0 | Original(s) | 0 | Duplicate(s)* |

7) X VOLUME Number: X1.1

7A) X VOLUME Media Count: X1.1A

8) Documents: 356h: Y Cover Letter: Y TOC: Y

RE: **Fenoldopam Mesylate Injection, USP 10 mg Base/mL**

*Note: "Duplicate" denotes that the media was removed from a reviewer's copy of the submission.

Total Electronic = Transport media with only 356h and the cover letter

Mixed = Transport media and one or more archival jackets containing additional documentation along with the 356h and the cover letter