DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

FEB 15 2000

Richard A. Shupack
Director
Legal Affairs - Regulatory
Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

RE: NDA#19-922
Corlopam (fenoldopam mesylate) Injection
MACMIS ID #8423

Dear Mr. Shupack:

Reference is made to Elan Pharmaceuticals' (Elan) January 7, 2000 letter, in response to a November 12, 1999 letter, from the Division of Drug Marketing, Advertising and Communications (DDMAC). Reference is also made to letters from Elan, dated November 29, 1999, and December 14, 1999, and a teleconference between Elan and DDMAC on December 20, 1999. These letters and teleconference concerned the dissemination of three homemade promotional pieces by or on behalf of Elan, that promoted Corlopam (fenoldopam mesylate) in violation of the Federal Food, Drug and Cosmetic Act and its implementing regulations. In our November 12, 1999 letter, DDMAC requested that you investigate the extent to which these homemade materials were used to promote Corlopam.

DDMAC has reviewed these materials and has determined that they promote Corlopam for unapproved uses, lack fair balance, and contain unsubstantiated cost effectiveness claims.

Unapproved uses

The Indication and Usage section of the approved product labeling (PI) for Corlopam states the following:

> Corlopam 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.

All of these homemade materials contain claims concerning the use of Corlopam for "renal protection." The following claims, although not an exhaustive list, exemplify claims presented in these homemade materials:

- IV Corlopam is "D-1" for cost-effective renal protection.

- Corlopam is indicated for short term (48 hrs.) treatment of hypertension and to increase renal blood perfusion; especially for patients with existing impaired renal function or in patients undergoing procedures that impairs [sic] renal function (i.e., patients receiving radiocontrast dyes, cyclosporine, or other vasoconstrictive agents).

- These beneficial renal effects make fenoldopam a useful agent for patients with renal dysfunction undergoing cardia [sic] or peripheral vascular surgery, both as a potential renoprotective agent and antihypertensive.

- Fenoldopam has recently gained FDA approval for renal indications.

These claims state, or imply, that Corlopam is useful in treating patients with renal impairment, or for renal protection, especially in those who are undergoing cardiovascular surgery or other procedures. However, these uses for Corlopam are not approved. Furthermore, your claim that "Fenoldopam has recently gained FDA approval for renal indications" is false. Therefore, your dissemination of these homemade promotional pieces constitutes promotion of Corlopam for unapproved uses.

In addition, in these homemade materials, you make dosing recommendations for renal indications. For example, you claim that "a dose of Corlopam 0.03-0.1 has been shown to increase renal perfusion without altering systemic blood pressure or heart rate in normotensive patients." This presentation is misleading because it makes representations that drug dosages recommended for use in the treatment of severe hypertension are safe and effective for the treatment of other classes of patients with different conditions. In addition, the Precautions section of the PI states that "Corlopam may occasionally produce symptomatic hypotension and close monitoring of blood pressure during administration is essential," and that "Corlopam causes a dose-related tachycardia, particularly with infusion rates above 0.1 mcg/kg/min."

Lack of fair balance

Although all of these homemade pieces contain efficacy claims, one of the pieces does not contain any risk information, and the other pieces contain minimal risk information, presented in a manner that is inadequate to convey the risks associated with the drug. Promotional materials must present information about the risks associated with the use of a drug in a manner reasonably comparable to that of claims concerning the drug's efficacy. Therefore, these materials are

lacking in fair balance because they fail to adequately disclose the risks associated with the use of Corlopam.

Unsubstantiated cost effectiveness claims

Two of these homemade pieces contain claims or implications that Corlopam is cost effective. For example, one piece presents the claim that "Corlopam is 'D-1' for cost-effective renal protection" and a second piece presents "expected outcomes" such as, decreased cost per discharge. These pharmacoeconomic outcomes have not been supported by adequate evidence. Therefore, your presentation of cost effectiveness claims is misleading.

In your January 7, 1999 letter, you acknowledged that certain Elan sales representatives have been involved in the development and/or dissemination of these violative homemade promotional materials. In addition, you described your policy for prohibiting use of homemade sales pieces, and specified the disciplinary and corrective actions taken to ensure that this activity will not recur.

DDMAC has reviewed your response and actions taken with respect to dissemination of these violative promotional materials. In light of your actions, DDMAC considers this matter closed. However, DDMAC will continue to closely monitor this issue and will consider alternative corrective measures if further activities occur.

If you have any questions or comments, please direct them to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding the issues raised in this letter, please refer to MACMIS ID # 8423 in addition to the NDA number.

Sincerely,

/S/

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

IV Corlopam (fenoldopam mesylate) is "D-1" for cost-effective, preventive strategy in patients with renal risk factors presenting for major Cardiovascular surgery.

Cost of 10 mg vial of IV Corlopam = $200 (added to 250 ml of diluent)

Infusion rates (ml/hour) to achieve a given drug dose rate (ug/kg/min) in patients with renal risk factors:

Body weight = 70 kg Drug dose rate (ug/kg/min) = 0.025 Infusion rate (ml/hr) = 2.64
TIME LENGTH OF INFUSION = 94 hours

Body weight = 70 kg Drug dose rate (ug/kg/min) = 0.05 Infusion rate (ml/hr) = 5.4
TIME LENGTH OF INFUSION = 46 hours

Body weight = 80 kg Drug dose rate (ug/kg/min) = 0.025 Infusion rate (ml/hr) = 3.0
TIME LENGTH OF INFUSION = 83 hours

Body weight = 80 kg Drug dose rate (ug/kg/min) = 0.05 Infusion rate (ml/hr) = 6.0
LENGTH OF INFUSION = 42 hours

Body weight = 90 kg Drug dose rate (ug/kg/min) = 0.025 Infusion rate (ml/hr) = 3.36
TIME LENGTH OF INFUSION = 74 hours

Body weight = 90 kg Drug dose rate (ug/kg/min) = 0.05 Infusion rate (ml/hr) = 6.6
TIME LENGTH OF INFUSION = 38 hours

Body weight = 100 kg Drug dose rate (ug/kg/min) = 0.025 Infusion rate (ml/hr) = 3.78
TIME LENGTH OF INFUSION = 66 hours

Body weight = 100 kg Drug dose rate (ug/kg/min) = 0.05 Infusion rate (ml/hr) = 7.8
TIME LENGTH OF INFUSION = 32 hours

IV Corlopam is "D-1" for cost-effective renal protection.

Please refer to Package Insert for full prescribing information.

Introduction

Fenoldopam is a selective dopamine$_1$ receptor agonist approved for the in-hospital, short-term (less than 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is indicated. Fenoldopam has demonstrated efficacy comparable to nitroprusside, but unlike nitroprusside, fenoldopam has no risk of cyanide toxicity and tends not to produce exaggerated swings in blood pressure Fenoldopam has recently gained FDA approval for renal indications. After cardiac surgery, acute renal failure requiring dialysis develops in up to 5% of patients and is associated with increased morbidity and mortality. Estimates of post-operative renal dysfunction approach 30% among cardiac surgery patients in some series. A similar renal outcome is noted in patients undergoing major vascular surgery. Patients treated with fenoldopam experience a significant increase in urinary flow and excretion of sodium and potassium with measurable increases in RBF and GFR. These beneficial renal effects make fenoldopam a useful agent for patients with renal dysfunction undergoing cardia or peripheral vascular surgery, both as a potential renoprotective agent and antihypertensive.

Current Pharmacy Guidelines for Fenoldopam Use

Criteria for Use.

I Surgery Type
- a. Cardiac
- b. Peripheral Vascular

II Authorized Prescribers
- Anesthesiologists

III. Patient Characteristics
- a Age > 70
- b. Pre-operative serum creatinine $\geq$1.2 in females or $\geq$ 1.4 in males
- c. History of IDDM
- d. History of CHF
- e History of previous myocardial revascularization
- f Catheterization with dye within the previous five (5) days

Guidelines for Administration

I. Dose -

1 Renal 0.03 µg/kg/min infusion

2 Antihypertensive
Initial: 0.03 - 0.1 µg/kg/min. titrated to achieve desired response.
Do not bolus, administer by continuous infusion.

Titration: Increase or decrease dose by 0.05 - 0.1 µg/kg/min at 15 minute intervals and less frequently as goal pressure is approached.

Discontinuation: Fenoldopam may be discontinued abruptly or tapered off

II. Duration: Fenoldopam should be continued no longer than 48 hours. Oral agents may be started prior to discontinuation for BP control

III Monitoring: Fenoldopam has been safely administered without the use of intra-arterial blood pressure monitoring. Frequent blood pressure monitoring is recommended (at least every 15 minutes in the absence of a-line monitoring).

Fenoldopam causes a dose-related tachycardia at rates above 0.1 mcg/kg/min.

Serum potassium may be decreased after as little as 6 hours of therapy. Levels should be monitored and potassium supplemented as indicated.

Expected Outcomes:

a. Decreased utilization of dialysis as measured by percentage of patients requiring dialysis post-cardiac or peripheral vascular surgery compared to baseline.
b Decreased ICU LOS
c. Decreased hospital LOS
d. Reduced diuretic requirements
e Decreased cost per discharge

FENOLDOPAM IS CURRENTLY AVAILABLE FOR YOUR USE IN THE SPOR.
10 mg and 20 mg AMPULES ARE STOCKED IN THE SPOR SATELLITE PHARMACY

FURTHER QUESTIONS / QUERIES CONTACT :
PATRICK SULLIVAN AT NEUREX - (203) 746-0993

OR FEEL FREE TO DISCUSS WITH DR. WHO HAS BEEN USING FENOLDOPAM IN THE CARDIAC OR'S FOR SEVERAL MONTHS.

- *Side effects / precautions:*
  The most common side effects are flushing, nausea, headache, and hypotension. Corlopam transiently elevates intraocular pressure. It can also cause reflex tachycardia and hypokalemia.

- *Compatibility with other drugs:*
  Corlopam is compatible with heparin, nipride, Epinephrine, gentamicin, lidocaine and cefazolin. Please do not run lasix in the same line since it can crystallize. B-blockers have an additive anti-hypertensive effect when given with Corlopam. Simply use 30-40% less Corlopam when a B-blocker is given. (Same starting dose)

- *Drug Interactions:* (NONE)
  There are known drug interactions.

- *Special Considerations:*
  Caution should be used in patients with known sodium metabilsulfate sensitivities.

  Corlopam can be infused peripherally.

  Corlopam is pregnancy Category B.

  Corlopam can be administered without the need for intra-arterial blood pressure monitoring.

- *How Mixed:*
  Corlopam comes in 1ml (10mg), 2ml (20mg), and 5ml (50mg) ampules. It must be diluted in 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection to achieve to achieve a 40ug/ml Concentration. *

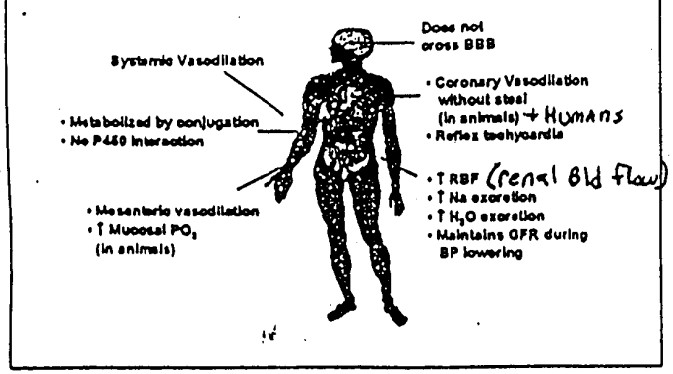
  * Example: 1ml (10mg) in a 250ml diluent = 40ug/ml
    or 2mL(20mg) in 500mL = 40ug/mL
  * Please see full prescribing information in package Insert enclosed for Corlopam.

FENOLDOPAM USAGE GUIDELINES

INDICATION	CRITERIA
<FORMULARY>	
A. Cardiac surgery or Vascular surgery	HTN & Creatinine clearance ≤ 50 cc/min and at least two of the following • Age ≥ 65 • Redo cardiac surgery • Presence of IABP • Presence of IDDM • Presence of peripheral vascular disease • History of prior nephrotoxin treatment ie. cyclosporin or ampho B (within past 6 months) • Potential for sodium nitroprusside toxicity or decreased organ perfusion
B. Hypertension	Patients requiring anti-hypertensive therapy in the presence of renal insufficiency, liver failure, surgery involving crossclamping of the aorta or having potential for sodium nitroprusside toxicity. (LFT's 2x normal, Cr clearance ≤ 50cc/min)
AREAS OF USE	1. Operating room 2. Intensive Care Unit 3. Emergency Dept
RESTRICTIONS	Patients with documented/known history of glaucoma
DOSAGE SUGGESTED	.03 – 1.6 mcg/kg/min

See dosing inside →

Physiologic Effects Fenoldopam



SLIDE D6

- Fenoldopam's activation of dopaminergic receptors on the proximal and distal renal tubules inhibits sodium reabsorption and results in diuresis and natriuresis, whereas activation of the renal vascular receptors in both afferent and efferent glomerular arterioles results in an increase in renal blood flow. In general, glomerular filtration rate increases in hypertensive patients and is maintained in normotensive patients.
- Animal studies indicate that fenoldopam also causes vasodilation in the splenchnic and coronary vascular beds.
- A study in dogs with experimental occlusion of the left anterior descending coronary artery demonstrated that fenoldopam improved the perfusion of normal and ischemic borderline myocardium.
- A study in pigs demonstrated a dose-dependent increase in gut mucosal oxygenation with fenoldopam.

✓ References

Shi Y, Zalewski A, Brovetto B, et al. Selective dopamine-1 receptor agonist augments regional myocardial blood flow: comparison of fenoldopam and dopamine. Am Heart J 1992;124:418–423.

Shusterman NH, Elliott WJ, White WB. Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. Am J Med 1993;95:161-168.

Germann R, Heisbeder W, Helskjold M, et al. Dopamine-1-receptor stimulation and mucosal tissue oxygenation in the porcine jejunum. Crit Care Med 1995;23:1500-1506.

Corlopam (fenoldopam mesylate)

- *Indications for use:*
  Corlopam is indicated for short term (48 hrs.) treatment of hypertension and to increase renal blood perfusion; especially for patients with existing impaired renal function or in patients undergoing procedures that impairs renal function. (i.e. patients receiving radiocontrast dyes, cyclosporin, or other vasoconstrictive agents)

- *Mechanism of action:*
  Corlopam is an arterial vasodilator with direct vasodilating action on renal, coronary messenteric, and peripheral arteries. It is a *selective* dopamine D1 agonist. It has no alpha, beta or D2 effects at any dose.

- *Onset/offset:*
  5 minute onset
  10 minute offset

✓ STARTING Dose FOR HTN →

- *Antihypertensive dosage range:*
  Start at 0.1 ug/kg/min. Higher initial starting doses will cause faster onset of antihypertensive effect. The maximum dose is 1.6 ug/kg/min.
  - no dose adjustment is needed for renal or hepatic impairment. (see PI enclosed)

✓ Titrating →

- *How to titrate to reach desired BP:*
  Titrate Corlopam in increments of 0.05 to 0.1 ug/kg/min q 15 minutes.

✓ RENAL DOSE

- *Renal dose:*
  A dose of Corlopam 0.03-0.1 has been shown to increase renal perfusion without altering systemic blood pressure or heart rate in normotensive patients.