CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	**19-922 SE5 005**
Submission Dates:	9/30, 11/25, 12/24 2003, and, 3/2 2004
Drug Name:	Corlopam (fenoldopam)
Applicant:	Abbott Laboratories
Submission:	Supplemental NDA
Reviewers:	Elena V. Mishina, Ph.D.
	Atul Bhattaram, Ph.D.

EXECUTIVE SUMMARY

The original NDA 19922, Corlopam (fenoldopam mesylate), a potent systemic and renal vasodilator, was approved in 1997 in adults 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. In the clinical trials for adults, doses from 0.01-1.6 µg/kg/min have been studied. Abbott is seeking an approval of Corlopam for the pediatric population (from 1 month to 12 years of age) for the same indication.

1. In the pediatric patients (<1 to 12 years), the mean half-life, volume of distribution and clearance are 3.36 min, 0.23 L/kg and 3.06 L/h/kg, respectively.
2. In the adult patients, the mean half-life, volume of distribution and clearance are about 4.4 min, 0.183 L/kg and 3 L/h/kg, respectively.
3. In the pediatric patients (<1 to 12 years), a 0.8 mcg/kg/min dose of fenoldopam infused over 30 minutes decreased mean arterial (MAP), diastolic (DIA), and systolic (SYS) blood pressures by 10, 8, and 9 mmHg on average, respectively, and increased HR by 13 bpm. These changes are placebo corrected.
4. In adult patients with mild to moderate hypertension, after a dose of 0.8 mcg/kg/min over 30 minutes, placebo corrected systolic and diastolic blood pressure decreased by 20 and 14 mmHg and HR increased by 21 bpm.
5. The sponsor has clearly shown that doses higher than 0.8 mcg/kg/min do not offer any additional benefit. For similar exposures (per kg doses or concentrations) pediatrics had smaller changes in blood pressure and HR compared to adults. In spite of the similar PK after per kg doses, administering higher per kg doses of fenoldopam in pediatrics (<12 years) is reasonable.
6. The sponsor studied doses of 0.05, 0.2, 0.8 and 3.2 mcg/kg/min in the pediatrics. However, the sponsor proposed doses of 0.2, 0.5, 0.8, 1.0, and 1.2 mcg/kg/min to be included in the labeling. Doses higher than 0.8 mcg/kg/min did not show any additional benefit, and they are not recommended. Taking into consideration the dose-response relationship, the fact that the onset of effect is rapid and that in clinical practice doses are titrated to effect interpolating between studied doses seems reasonable. Therefore, doses of 0.2, 0.5, and 0.8 mcg/kg/min are recommended for children under the age of 12 years.

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I has reviewed the information included in the sNDA 19-922. The information provided in the Supplement No. SE5 005 to NDA 19-922 for Corlopam Injection ampule is appropriate to evaluate the pharmacokinetic and pharmacodynamics in pediatric patients.
The Office of Clinical Pharmacology and Biopharmaceutics recommends adopting the proposed language for the labeling.

LABELING RECOMMENDATIONS

(b□ (4)----------

-

-
-- □ ----------

-
-- □ ----------

-

_____ Date_____
Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

_____
Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on March 4, 2004

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

/s/

Patrick Marroum
3/9/04 02:24:17 PM

Jogarao Gobburu
3/17/04 09:36:49 AM