Clinical Review for NDA 19-922

Executive Summary

This submission consists of a single study (# 2000-027) in pediatric patients. This study explores the relationship between fenoldopam infusion or concentrations and change in vital signs (MAP, DBP, SBP and heart rate). Data was available for 76 of the 77 pediatric subjects enrolled (one child received no infusion because of pump malfunction and the results from this child was excluded). These subjects ranged in age from <1 month to < 12 years or < Tanner stage 3. The majority of these subjects were undergoing surgical procedures for which controlled-hypotension was desired.

These subjects were treated, in a double-blind manner for 30 minutes with either placebo or fenoldopam at one of four doses (0.05, 0.2, 0.8 or 3.2 ug/kg/min). The double-blind infusion was started only after the subject had anesthesia induced with stable vital signs for surgical patients or whose status was stable for non-surgical patients. The results from the double-blind portion of the study indicate fenoldopam-treatment decreases MAP, DBP and SBP but increases heart rate in a dose-related manner compared to placebo. At the end of the double-blind phase, subjects were treated in an open-label manner with drug to target MAP measurement. Vital signs were continuously collected. During the open-label phase, subjects were started at a dose of 0.1 u/kg/min with titration based on blood pressure response every 20-30 minute, with increases limited to 0.3 to 0.5 ug/kg/min. All subjects had a blood sample for fenoldopam measurements done immediately prior to and five minutes after discontinuation of the infusion. Additional samples for those > 2 years were also collected at 15-30 minutes after discontinuation and also during stable (60 minutes) steady infusion during the steady state phase. A model relating kinetics to dynamics was produced incorporating both the blinded and open-label portions of this study.

The results per sponsor for the pharmacokinetic/pharmacodynamic model are included in this review. The FDA analysis has not yet been finalized (see the biopharmaceutic review by Dr. E. Mishina).

I. Recommendations

A. Recommendation on Approvability

The submission is approvable. Corlopam can be recommended for short-term use to afford modest decreases in blood pressure in a pediatric population at a dose of between 0.2 and 0.8 ug/kg/min.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

None required.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical program consists of a single study # 2000-027. The study enrolled 77 patients (76 with available data), that initially received, in a double-blind manner, either placebo or fenoldopam at one of four doses (0.05, 0.2, 0.8 or 3.2 ug/kg/min). Subsequently, subjects then received in an open-label manner fenoldopam infusions with continuous monitoring of vital signs. There was a 30-minute washout period after the completion of the open-label infusion.

B. Efficacy

Based on a double-blind portion of the study, there is a dose-related and rapid in onset decrease in blood pressure compared to pre-infusion baseline. There is also an increase in heart rate, which is also rapid in onset. The

placebo-subtracted effects at the 0.8 and 3.2 ug/kg/min for DBP/SBP are –8.4 to –5.8 / -9.2 to –7.6 mm Hg. Heart rate was increase over placebo by 12.5 to 20 BPM for the placebo subtracted values.

Table 1: ANCOVA results double blind, dose-ranging portion of the study for vital signs

Parameter	p-value		Fenoldopam (ug/kg/min)			
		PBO	0.05	0.2	0.8	3.2
DBP						
N=	P=0.012	16	15	16	15	15
LSMean ± SD		0.2 ±2.5	1.1 ± 2.6	-1.7 ± 2.5	-8.2 ± 2.7	-5.6 + 2.6
Median		-1.0	0	-2.0	-13.0	-6.0
LS Mean PBO Subtracted		0	0.9	-1.9	-8.4	-5.8
SBP						
N=	P=0.021	16	15	16	15	15
LSMean ± SD		-2.6 ±3.5	-0.04 ± 3.65	-2.97 ± 3.5	-11.8 ± 3.7	-10.2 + 3.7
Median		-2.5	-3.0	-4.5	-16	-9.0
LS Mean PBO Subtracted		0	+2.56	-0.37	-9.2	-7.6
Heart rate						
N=	<0.001	16	15	16	15	15
LSMean ± SD		-5.7 ± 4.2	-4.4 ± 4.27	4.8 ± 4.12	6.8 ± 4.3	14.3 + 4.3
Median		-3.5	-6.0	0	6.0	8.0
LS Mean PBO Subtracted		0	1.3	10.5	12.5	20

- ANCOVA results with an LOCF imputed value for missing data. Baseline was the covariate.

The persistence of effects for fenoldopam in children was not assessed by a randomized withdrawal study. However, among those who received fairly high doses of fenoldopam (> 0.8 ug/kg/min) for at least one hour, there was a increase in blood pressure of approximately 9- mm Hg and an decrease in heart rate of 10 BPM during the 30 minutes after cessation of the infusion. These values re- approached but did not quite attaining baseline measurement.

The magnitude of blood pressure effects appears to be substantially greater in adults than children (approximately –20/26 mm Hg in adults, based on current Corlopam label). Heart rate increase in adults (+ 20 BPM) is the same as in children.

There is no data that indicates that fenoldopam-induced hypotension demonstrates any clinically meaningful benefits such as diminishing blood loss or preventing wound dehiscence.

C. Safety

The only interpretable safety data is derived from the 30-minute double-blind phase. During this period adverse events appear to be an extension of the pharmacologic effect of drug. Since all subjects received fenoldopam during the open-label phase there is no control group to for comparison of adverse events rates.

There were two deaths among those treated with fenoldopam during the open-label phase. One subject had suffered hypoxic encephalopathy prior to the start of the infusion that either progressed or followed its natural course. The subject was noted on day 3 to have no cerebral activity or cortical response to pain. The subject was declared brain-dead and became an organ donor. The second subject was a newborn who completed the infusion and had an intracranial hemorrhage after the use of TPA for unclogging a venous cannula (ECMO).

One publication [1] suggests that PaO2 decreased from 232 ± 7 mm Hg to 199 ± 11 mm Hg during the fenoldopam infusion 6-patients undergoing posterior spinal fusion. Upon discontinuation of the fenoldopam

[1]Tobias JD' "Fenoldopam for controlled hypotension during spinal fusion in children and adolescents", Paediatr Anaesth, 2000 10(3) :261-6.

infusion, the oxygenation returned to baseline. The authors suggest that fenoldopam may impair hypoxic-pulmonary vasoconstriction.

D. Dosing

The dose range in children appears to span from 0.2 ug/kg/min to 0.8 ug/kg/min. The lowest dose studied during the dose-ranging study, 0.05 ug/kg/min was not differentiable from placebo with respect to a blood pressure effect. The highest dose studied (3.2 ug/kg/min) did not appear to offer any benefit in blood pressure response than the 0.8 ug/kg/min infusion rate but did provoke greater tachycardia. The recommended dose in adults is 0.1 to 1.6 ug/kg/min. During open-label infusion doses as high as 4.0 ug/kg/min have been occasionally administered.

E. Special Populations

This study enrolled neonates (if > 2 kg), infants, toddlers, pre-school and school aged children who were < 12 years and also < Tanner 3. Approximately 44 % of those enrolled were under two years old; 44 % were male and approximately 22% were black. See the biopharmaceutic review for the relationship of such parameters with kinetics or dynamics.

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The drug is currently marketed as Corlopam and is approved for the use in adults. The highest labeled dose in adults is labeled as 1.6 ug/kg/min.

B. State of Armamentarium for Indication(s)

None of the currently approved afterload reducers is currently approved for pediatric use.

C. Important Milestones in Product Development

This supplement was originally submitted on Sept 20, 2002 in response to a written request dated March 25, 2002. The sponsor subsequently withdrew this submission on Dec 11, 2002. The reason for withdrawal was the inability to confirm the data from a single study site in a second study. The application was resubmitted without the unvalidated study.

D. Other Relevant Information

None

E. Important Issues with Pharmacologically Related Agents

None

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There was no new information from chemistry, animal pharmacology, toxicology or statistics. The biopharmaceutic review is ongoing and the conclusions are not yet available for inclusion into this review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The pharmacokinetic parameters are derived from three sources: the first is the concentration derived from the double blind portion of the study, specifically the concentration of fenoldopam at the 20-minute time point (Figure 1). The concentration at this time point was linearly dependent on infusion rate. Please see the review by the biopharmaceutic reviewer for the effect of age. There were only a small number of blacks in each treatment group to draw meaningful conclusions (1-5 per group).

Figure 1 : Concentration versus infusion rates

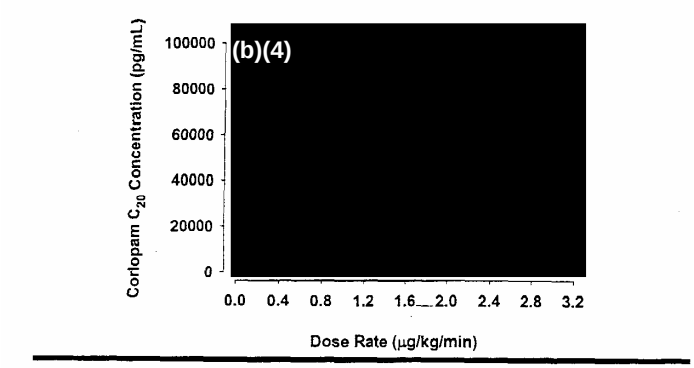

Figure 11.5.b Individual Fenoldopam Plasma Concentration (C_{20}) versus Dose Rate

A second set of data was the clearance data calculated from the decline in concentration upon discontinuation of the infusion. The elimination measurements were available for only 53 patients for a two-point (0 and 5 minutes post infusion) estimate and 56 for estimates derived from additional or other points. Fenoldopam concentrations rapidly decline in children with a half-life of approximately 3-5 minutes. These results are somewhat faster than in adults (6.6 minutes).

Table 2: Elimination constants from end of infusion data

	Children		Adults
	2-point (N=53)	All data (N=56)	
Elimination rate constant l/hr	12.37 ± 5.44	9.19 ± 4.09	9.05
T ½ (min)	3.36	4.53	6.6

Additional kinetic analysis from all concentration measurements derived from the double blind, open-label and washout parts of the study are included in the biopharmaceutic review.

B. Pharmacodynamics

The dose-related effect of fenoldopam on vital signs is tabulated in Table 1, above. Maximum effects are modest (PBO-subtracted). DBP/SBP values were approximately –8.4 to –5.8 / -9.2 to –7.6 mm Hg at the 0.8 and 3.2 ug/kg/min infusion rates, respectively. Heart rate increased with dose and reached a PBO-subtracted maximum of approximately 20 BPM at the 3.2 ug/kg/min. The magnitude of blood pressure effect is substantially less than that observed in mild-moderate hypertensive adults (-26/-20 mm Hg per current label). The increase in heart rate of 20 BPM approximates that in adults (19 BPM).

There was no randomized withdrawal phase to establish persistence of drug effect. The persistence of effect can be deduced by the response of blood pressure and heart rate after the completion of the infusion among patients who had higher doses of fenoldopam (N= 44). By thirty minutes after the cessation of the infusion, mean arterial blood pressure increased approximately 9 mm Hg and heart rate decreased by 10 BPM and re-approached but not completely reach baseline values.

Additional information as to dynamic parameters may also be ascertained from the results of modeling the data throughout the entire infusion period and the 30 minutes after the end of the infusion. See the biopharmaceutic review (the review is not yet available).

IV. Description of Clinical Data and Sources

A. Overall Data

The data consisted of the 28 volumes of the study report (24 of these were submitted as clinical). Volumes 27 and 28 contained case reports for deaths and some (but not all) dropouts.

B. Tables Listing the Clinical Trials

Only a single trial was submitted Study # 2000-027.

C. Postmarketing Experience

There is no post-marketing experience in children.

D. Literature Review

A "PUBMED" search was performed for "fenoldopam" AND "Children". There were six references cited. Two references [1, 2] appear relevant as clinical experience of the use of fenoldopam in pediatric patients. Neither references contained controlled studies and, therefore, add little additional information with the exception of a safety issue on the ability to oxygenate.

V. Clinical Review Methods

A. How the Review was Conducted

This review was based on the 28-volume submission dated September 30, 2003. Still pending is the analysis by the biopharmaceutic review team. The current label of fenoldopam was consulted to assess the magnitude of the effect of Corlopam in adults.

B. Overview of Materials Consulted in Review

The review was based on the submitted data. Safety also reflects the issue raised in reference [1].

C. Overview of Methods Used to Evaluate Data Quality and Integrity

One study site (Lavondowsky) (as evaluated by DSI. No major deficiencies were noted which would compromise the integrity of the results frbm that site.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials appeared to be performed ethically.

E. Evaluation of Financial Disclosure

The financial disclosure information is adequate. Valentine Yien, the VP and controller of Abbott Laboratories, Hospital product Division, submitted a signed FDA form 3454 asserting that no financial arrangements were entered into with the clinical investigators. The form also stipulates that no investigator received significant payments.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Fenoldopam is useful for the short-term and modest reduction of blood pressure in a pediatric population.

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[2] Strasser LM, Pruitt RD, Tobias JD "Initial experience with fenoldopam in children"; Am, J. Ther, 1999; 6 (5) 283-8.

B. General Approach to Review of the Efficacy of the Drug

The efficacy is engendered in the results of study 2000-027.

C. Detailed Review of Trials by Indication

A review of the single follows.

D. Efficacy Conclusions

The results of this study suggest that fenoldopam is useful for the short-term and modest decrease in blood pressure in a pediatric population. The useful dose range approximates that in adults. For pediatric patients a range of 0.2 to 0.8 ug/kg/min can be recommended. The useful range in adults is between 0.1 to 1.6 ug/kg/min. The magnitude of the effect on blood pressure in the dose-ranging double-blind portion of the study

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety database is the safety results from study 2000-027.

B. Description of Patient Exposure

The extent of exposure is shown below. The mean duration of exposure was slightly longer than 3 hours.

Table 3: Exposure duration, dose and average dose by age group > and < 2 years old

	Neonate, infants and toddlers (< 2 years) N= 34	Pre-school and school age (≥ 2 years) N= 43
Time (hours, Mean ± SE) [Range]	2.88 ± 0.96 [0.82- 4.83]	3.46 ± 1.58 [0.50-6.75]
Cumulative dose (ug/kg, mean ± SD) [Range]	202.57 ± 158.8 [9.9- 702]	214.4 ± 197.8 [0.15-991.5]
Average Dose (ug/kg/min, mean ± SD) [Range]	1.06 ± 0.62 [0.09-2.42]	0.75 ± 0.70 [<0.005- 3.20]
Maximum Dose (ug/kg/min, mean ± SD)[Range]	2.08 ± 1.17 [0.10-4.10]	1.73 ± 1.13 [< 0.005- 3.96]

C. Methods and Specific Findings of Safety Review

Adverse events were derived from the sponsor's tabulated summaries. Case reports for deaths were available (2 deaths). In addition, case reports for some patients with serious adverse events were also available and were reviewed.

D. Adequacy of Safety Testing

The safety of the use of fenoldopam in pediatrics is largely predicated on the safety in adults. The only interpretable safety data of fenoldopam in children is derived from the double blind, placebo-controlled dose ranging phase. This phase lasted only 30 minutes. Any events, which occurred after the end of the double-blind period even if associated with the 30-minute infusion, could not be interpreted either as being attributable to drug or as a consequence of the underlying disease process or surgical treatment. The modest size of the study further any meaningful interpretation of any of the observed adverse events.

E. Summary of Critical Safety Findings and Limitations of Data

The main interpretable adverse events are excessive pharmacological responses (hypotension and tachycardia).

VIII. Dosing, Regimen, and Administration Issues

Fenoldopam should be diluted in normal saline. The drug should be infused by a pump appropriate for the volumes needed in children and also appropriate to assure that the drug is infused at a constant (not pulsatile) manner. The dose of fenoldopam in children is between 0.2 to 0.8 ug/kg/min. Titration can begin at an infusion rate of 0.1 ug/kg/min with increases of 0.3 ug/kg/min every 10 –20 minutes (based on a half-life of 3-5 minutes).

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor did not analyze the results based on gender. Since all children were pre-pubertal (< Tanner 2), it would not be anticipated that gender would be a meaningful parameter.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The effects of age will be addressed in the biopharmaceutic review. There were too few blacks per treatment group (1 to 5) to assess the effect of race on effect.

C. Evaluation of Pediatric Program

The pediatric program is the essence of this submission.

D. Comments on Data Available or Needed in Other Populations

None.

X. Conclusions and Recommendations

A. Conclusions

Fenoldopam is useful for the short-term use to effect modest reductions in blood pressure in children <12 years. Tachycardia is the most obvious adverse event.

B. Recommendations

The drug is approvable for use in pediatrics for short-term use (purposefully left ambiguous as to the duration of use).

XI. Appendix

A. Other Relevant Materials

Two publications were reviewed. The two publications contained data from a total of 16 subjects (six subjects in Reference 1 and ten subjects in reference 2). who were treated with fenoldopam to induce controlled hypotension. Since the results are uncontrolled, there is little that can be concluded.

B. Individual More Detailed Study Reviews (If performed)

See below.

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