

The weight of the F1 adults also showed consistent differences from the control groups. After weaning, the pups of drug-treated dams did not gain as much weight as the pups of the saline control dams. Pups from the Intralipid-exposed dams also did not gain the same amount of weight as did the saline control group. This effect was primarily in the male F1 generation. The female F1 animals showed little difference from the control offspring.

Table 22 Group Mean Body Weights (g)

		F1 Generation - Adults													
		Males													
		Group 1 - Saline Control							Group 3 - Clevidipine 13 mg/kg/day						
		Group 2 - Intralipid Control							Group 4 - Clevidipine 35 mg/kg/day						
Group	Summary Information	28	35	42	49	56	63	Day							
								70	77	84	91	98	105	112	119
1 *&	Mean	101.8	163.0	226.1	292.1	352.1	400.6	440.2	472.6	497.7	517.0	538.3	559.5	584.1	610.8
	S.D.	10.2	15.1	20.2	25.8	31.0	34.0	39.9	42.7	47.8	47.6	50.4	51.6	55.0	52.1
	N	22	22	22	22	22	22	22	22	22	22	22	22	22	17
2 *&	Mean	94.1	153.4	214.3	277.1	330.4 A	375.3 A	407.7 A	434.6 B	457.3 E	473.7 E	494.3 E	515.3 E	535.9 B	552.6 B
	S.D.	6.7	11.0	14.7	16.9	18.6	20.9	21.5	24.4	26.0	24.7	25.5	25.4	28.8	32.5
	N	17	17	17	17	17	17	17	17	17	17	17	17	17	14
3 &&	Mean	94.0	150.8	211.2	273.6	328.0 A	367.8 B	404.5 B	441.9	468.3	488.7	507.4	528.4	550.1	582.6
	S.D.	12.2	17.5	22.3	26.1	28.6	29.3	33.1	38.8	43.1	40.5	43.4	43.8	48.0	52.9
	N	13	13	13	13	13	13	13	13	13	13	13	13	13	9
4 &&	Mean	97.4	154.4	212.8	275.6	331.8	374.4	406.4	447.6	488.0	504.2	527.2	550.8	577.4	599.8
	S.D.	6.7	10.5	15.3	16.6	25.8	34.7	29.0	31.0	17.9	20.4	21.6	23.8	23.0	29.2
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	4

Significantly different from control group (group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett) D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)
 Significantly different from control group (group 2) value: a - P ≤ 0.05 b - P ≤ 0.01 c - P ≤ 0.001 (Dunnett) d - P ≤ 0.05 e - P ≤ 0.01 f - P ≤ 0.001 (Dunn)

*&: Subset 2
 &&: Subset 1 and 2

APPEARS THIS WAY
 ON ORIGINAL

Although there were 2 early time points when weight gain was lower than that of controls, no obvious pattern in gestational weight gain was seen for the F1 females.

Table 26 Group Mean Body Weight Gains (g) of Females During Gestation

		F1 Generation						
		Group 1 - Saline Control Group 2 - Intralipid Control			Group 3 - Clevidipine 13 mg/kg/day Group 4 - Clevidipine 35 mg/kg/day			
		Day of Gestation						
Group	Summary Information	From: 0	6	9	12	15	18	20
		To: 6	9	12	15	18	20	
1 *&	Mean	29.0	12.1	13.9	17.1	34.0	25.5	
	SD	5.9	4.9	5.1	4.2	6.3	15.1	
	N	22	22	22	22	22	22	
2 *&	Mean	23.9 A	10.4	15.9	19.3	37.9	25.5	
	SD	5.6	5.7	3.6	4.8	5.1	10.5	
	N	15	15	15	15	15	15	
3 &&	Mean	30.6 b	11.1	18.1 A	17.9	41.1 B	27.1	
	SD	5.4	5.3	4.8	6.4	7.6	8.8	
	N	23	23	23	23	23	23	
4 &&&	Mean	27.1	9.6	18.4	15.9	41.4	22.6	
	SD	9.8	5.5	7.0	2.7	11.1	6.1	
	N	7	7	7	7	7	7	

Significantly different from control group (group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett) D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)
Significantly different from control group (group 2) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (Dunnett) d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Dunn)

*&: Subset 2
&&: Subset 1 and 2

There were no obvious gross necropsy findings in the F1 animals.

**APPEARS THIS WAY
ON ORIGINAL**

There was an apparent trend in the reproductive performance of the F1 animals. Mating index, fertility index and conception rate decreased in adults who had early exposure to clevidipine.

Table 37 Group Mean Parental Performance

Group	Number Placed for Mating		Number Mating	F1 Generation - Adults		Mating Index (%)	Fertility Index (%)	Conception Rate (%)	
	Males	Females		Mean (SD) Day to Mating	Group 3 - Clevidipine 13 mg/kg/day Group 4 - Clevidipine 35 mg/kg/day				
					Number Females Pregnant				
1*&	22	22	22	4.8 3.01 (N: 22)	22	100.0	100.0	100.0	
2*&	17 a	18	18	4.2 2.88 (N: 15)	18	100.0	100.0	100.0	
3 &&	25 b	26	26	3.6 2.31 (N: 25)	24	100.0	96.0	92.3	
4 &&	8 c	10	9	4.1 2.85 (N: 8)	8	87.5	75.0	88.9	

a = Male 226 paired with females 270 and 280
 b = Male 303 paired with females 356 and 366
 c = Male 404 paired with females 455 and 459 and male 409 paired with females 456 and 458
 Significantly different from control group (group 1) value: X - P ≤ 0.05 Y - P ≤ 0.01 Z - P ≤ 0.001 (Wilcoxon - day to mating only)
 Significantly different from control group (group 1) value: * - P ≤ 0.05 ** - P ≤ 0.01 *** - P ≤ 0.001 (Fisher's)
 Significantly different from control group (group 2) value: x - P ≤ 0.05 y - P ≤ 0.01 z - P ≤ 0.001 (Wilcoxon - day to mating only)
 Significantly different from control group (group 2) value: + - P ≤ 0.05 ++ - P ≤ 0.01 +++ - P ≤ 0.001 (Fisher's)
 *&: Subset 2
 &&: Subset 1 and 2

Given the small number of animals, it's difficult to say how real the effects are in either the parental or maternal summaries. The primary effect noted in maternal effects is a decreased pregnancy rate.

Summary of maternal effects

group	# mated females	# pregnant females	Preg rate (%)	Gestation index (%)
Saline	22	22	100	100
Intralipid	18	18	100	100
Clev 13mg	26	24	92	96
Clev 35mg	9	8	89	100

Viability and weight were apparently unaffected in the F2 generation. There is no record of any examination of the male reproductive tract of any generation beyond gross observation.

Discussion and Summary

Continuous intravenous administration of clevidipine in a lipid emulsion at doses of 13, 35 and 55 mg/kg/day caused dose-related increases in F0 maternal mortality, mostly in late gestation. The increased mortality was primarily related to complications with parturition, most likely due to interference with uterine contractions, an effect reported with other calcium channel blockers such as nicardipine. In this study, no maternal NOAEL was identified. Dose-related gross pathology was associated with the infusion sites, lung, adrenals, liver and spleen. The sponsor attributed these findings to the drug.

Evaluation of the F1 generation was somewhat compromised by how few members of the F1 generation survived. F1 viability (PN days 0-4) showed a dose-related decrease and an effect from the lipid vehicle.

There were slight decreases in the time for F1 drug-treated pups to reach the day of tooth eruption and eye opening. F1 females showed a slight increase to the time of vaginal opening. The significance, if any, of these observations is unclear.

Fertility in the F1 generation was apparently decreased in those pups who had received early exposure to clevidipine. Unfortunately there is no record of any histologic examination of the male reproductive tract nor assessment of sperm characteristics.

A 14-day intravenous infusion toxicity study of clevidipine in the male Beagle dog with a 28-day recovery period.

Study location: _____

Study number: Project number 500943

Study initiated: dosing started March 31, 2005

GLP: statement included

QA: yes

Test article: KV1348

The study design is summarized in the sponsor's table reproduced below.

Group	Dose (mg/kg/day)	Conc (mg/ml)	Dose rate (ml/kg/hr)	Animal number	
				main	recovery
Saline	0	0	1.84	4	2
20% lipid emulsion	0	0	1.84	4	2
clevidipine	6.8	3.0	0.19	4	2
clevidipine	16	3.0	0.44	4	2
clevidipine	66	3.0	1.84	4	2

In a previously conducted 28 day study testing the same dose levels proposed for the current study, dose-related decreases in absolute and relative testes weights were observed. No histopathology observations were noted in the testes other than those usually associated with immature dogs. This study was conducted in mature male Beagles to explore a possible testicular effect.

At the start of treatment, dogs were 13 months to 5 years of age and weighed 10.3 to 14.5 kg. Approximately 1 week after arrival, catheters were surgically implanted. Catheters were placed in the femoral vein and advanced to the vena cava. The end of the catheter was exteriorized over the nape of the neck.

Dosing began on consecutive days with approximately equal number of animals from each group being dosed on each day. The test/control articles were administered by continuous intravenous infusion for 12 hours daily for 14 consecutive days and continuously infused with saline during the non-dose periods. After completion of the treatment period, recovery animals were maintained un-dosed for a 28-day period.

Animals were observed daily for signs. Testicular size was measured with a caliper pretreatment and before scheduled necropsy. Body weight was measured weekly. Food consumption was recorded daily. Ophthalmic exams were conducted pre-treatment and during week 2.

Semen samples were obtained pre-treatment (before and after surgery) and assessed for volume, color and appearance. Four additional samples were obtained approximately 3 days apart to assess for volume, color, appearance, sperm concentration, motility and morphology.

Twice pretreatment and during weeks 2 and 6, hematology, clinical chemistry and urinalysis were performed on all animals. Fasting blood samples were used.

Necropsy : Gross observations were made and a standard list of tissues retained for histopathology. The methods section states that extra sections of the testes were collected and processed for stage-dependent qualitative evaluation of spermatogenesis.

**APPEARS THIS WAY
ON ORIGINAL**

Results

Analysis of dosing solutions: The analysis reported 2 impurities at retention times of and minutes. These same two impurities are reported as typically seen in the Standard Preparation. The impurity was identified as ——. Group 4 and group 5 samples had lower than expected values (out of specification results). Despite this, dose-related effects are apparent in the overall results of the study. However, page 285 vol. 7 stated that “The low and variable results are due to physical instability of these particular emulsion samples.”

Body weight summary

Summary of mean weights (kg) for main study

	saline	Lipid veh	Clevidipine mg/kg/day		
			6.8	16	66
Day -1	12.58±1.21	12.02±1.30	12.25±1.19	11.90±1.13	11.88±1.07
Day 7	12.42±1.25	12.42±1.32	12.48±1.32	12.08±1.04	12.03±1.16
Day 14	12.60±1.46	12.63±1.19	12.53±0.94	12.13±0.94	12.25±1.43

Summary of mean weights for recovery phase

	saline	Lipid veh	Clevidipine mg/kg/day		
			6.8	16	66
Day 21	13.15±2.19	12.50±1.98	13.20±0.99	11.70±0.42	12.15±1.34
Day 28	13.10±1.84	12.50±1.84	13.45±0.64	11.90±0.57	12.30±1.41
Day 35	13.30±1.70	12.60±1.70	13.50±0.57	12.00±0.28	12.15±1.34
Day 42	13.15±1.91	12.45±1.63	13.55±0.64	12.05±0.49	12.15±1.63

Food consumption was somewhat decreased in the lipid control group and MD and significantly decreased ($p < 0.01$) in the HD group within the first week. The sponsor took steps to encourage the dogs to eat by adding warm water and canned food to the diets. Food consumption did increase with some occasional fluctuations. There did not appear to be any problems with food consumption in the recovery period.

Reproductive assessments

The sponsor presents data on ejaculated volume and ejaculated sperm numbers pre surgery, post surgery, during treatment and during recovery. The numbers are very variable as could be expected and do not add to the informative value of the study.

The pre-treatment sperm morphology showed a great deal of variability. No historical ranges were provided. The data as to effects of treatment on morphology has little informative value. It also appears that there is a greater pre-treatment range of existing

effects in the dogs given clevidipine. Was there a bias in that older dogs were assigned to the drug-treated groups?

Sperm morphology: Reviewer's summary of percent effect or finding pre-treatment

Sperm morphology Finding	Saline control	Lipid control	Clevidipine mg/kg/day		
			6.8	16	66
Abnormal head range pre-tx	0-8	0-10	0-3	0-44	0-14
Abnormal acrosome range pre-tx	0-2.7	0-2	0-1.5	0-3	0-1
Abnormal mid-piece Range pre-tx	1-14	1-19	1-24	2-27	3-8
Abnormal tail Range pre-tx	1-21	0-29	1-46	2-59	0-38

Ophthalmology

The ophthalmologist's report noted no drug-related effects.

Hematology

There was a very slight decrease in neutrophils and corresponding increase in lymphocytes in the clevidipine-treated dogs. This change was seen in both percent and absolute numbers. However, the magnitude of change is so small as to be within the realm of variability.

	Parameter		
	RBC (10 ⁶ /dl)	Hb (g/dl)	Ht %
Saline control	6.89±0.69	15.35±1.88	45.58±5.26
Lipid control	6.32±0.22	14.45±0.29	42.40±1.04
Clev 6.8 mg/kg	6.08±0.88	13.30±1.85	39.97±5.86
Clev 16 mg/kg	5.88±0.41	12.93D±0.79	38.50D±2.31
Clev 66 mg/kg	5.47E±0.38	12.12Ed±0.97	36.10Ed±2.73

E= significantly different from saline control $p \leq 0.01$ Dunn's test

D= significantly different from saline control $p \leq 0.05$

e= Significantly different from lipid control $p \leq 0.01$

MCH and MCV were not affected. This appears to be a normocytic, normochromic blood loss anemia. However, there was no sign of a regenerative response.

Clinical Chemistry

Blood urea was increased in the clevidipine-treated animals but with no corresponding increase in creatinine. This is suggestive of animals being off-feed.

Summary of clinical chemistry changes Day 11 of treatment period

	Chol Mg/dl	Trig Mg/dl	Tprot g/dl	Glob g/dl	A/G
Saline control	147 ^c ±25	25±4	6.3±0.4	2.78±0.66	1.34±0.423
Lipid control	266 ^c ±21	34±2	6.7±0.5	3.23±0.73	1.13±0.416
Clev 6.8 mg/kg	160 ^c ±38	25±10	6.5±0.5	3.13±0.59	1.122±0.243
Clev 16 mg/kg	140 ^c ±21	18 ^c ±3	5.6 ^{Ac} ±0.4	2.12 ^b ±0.30	1.648 ^a ±0.245
Clev 66 mg/kg	195 ^{Ac} ±33	26±8	5.6 ^{Ac} ±0.3	2.27 ^a ±0.35	1.490±0.267

Significantly different from saline control: A p<0.05, B p<0.01, C p<0.001 by Dunnett's

Significantly different from lipid control: a p<0.05, b p<0.01, c p<0.001 by Dunnett's

d p<0.05, e p<0.01 by Dunn's

Summary of clinical chemistry changes Day38 of recovery period (n=2 dogs per group)

	ALT	A/G
Saline control	41±18	1.280±0.39
Lipid control	47±11	1.075±0.53
Clev 6.8 mg/kg	31±11	1.110 ±0.37
Clev 16 mg/kg	33±4	1.50±0.24
Clev 66 mg/kg	144±137	1.48±0.46

Urinalysis

Summary tables for urinalysis were not located. From the individual animal data I calculated group mean values for the various parameters analyzed numerically. However, there was a tremendous level of variability apparent in the pre-treatment data. It was difficult to discern consistent patterns.

**APPEARS THIS WAY
ON ORIGINAL**

Organ Weight Changes

Summary of organ weight findings at end of recovery period

	Testis absolute(g)	Spleen absolute(g)	Pituitary absolute(g)
Saline control	20.16±0.39	51.33±5.59	0.096±0.012
Lipid control	17.79±3.46	69.90±1.33	0.089±0.009
Clev 6.8 mg/kg	15.38±4.46	67.21±3.19	0.082±0.017
Clev 16 mg/kg	14.32±6.38	48.94±14.82	0.078±0.001
Clev 66 mg/kg	18.17±6.04	39.57±9.91	0.078±0.005

Summary of organ weights relative to body weight (%) : recovery period

	Kidney
Saline control	0.480±0.045
Lipid control	0.592±0.012
Clev 6.8 mg/kg	0.558±0.072
Clev 16 mg/kg	0.505±0.064
Clev 66 mg/kg	0.598±0.025

Histopathology

The pathologist's report noted drug-related cardiac lesions at doses ≥ 16 mg/kg.

Minimal to slight hemorrhage of the right atrium and/or pericardium and/or endocardium was present in 1/4 and 2/4 males at dosages of 16 and 66 mg/kg/day, respectively. Minimal to slight chronic inflammation, occasionally accompanying the hemorrhage, was seen in the right atrium and pericardium of 2/4 males at 66 mg/kg/day. Slight myocardial degeneration/necrosis of the papillary muscle and left ventricle was observed in 1/4 males at 66 mg/kg/day. These cardiac changes are compatible with drug-induced myocardial/atrial lesions that have been reported at high doses with anti-hypertensive drugs in the beagle dog¹.

The pathologist also noted that:

Male reproductive assessments were difficult to interpret due to individual variability, which was not influenced by the treatment. In many animals, regardless of their dose group, the collection was unsuccessful at many occasions or the ejaculated volume was too small to be analyzed or interpreted. In addition, many samples had no spermatozoa. However, in animals/sampling occasions where sufficient ejaculated volume/spermatozoa counts were produced, the administration of the vehicle with or without clevidipine did not have any effect on the sperm motility, spermatozoa counts or on the spermatozoa morphology.

There were unsuccessful semen collection attempts on the dogs who later were determined to have hypo/aspermatogenesis. The sperm count, motility and morphology were determined only on the ejaculated samples. Post-mortem, only histopathology was assessed. A determination of spermatozoa/unit weight would have been helpful. Also, the methods and protocol state that spermatogenic staging had been performed. I did not find any summary of findings nor did I find any reference to the findings.

The pathologist also adds a comment that the hypo/aspermatogenesis seen in 4 dogs (1LD, 1 MD and 2 HD) was suggestive of immaturity. They cite a report stating that up to 6% of Beagles 2.5-7.5 years show incomplete spermatogenesis (Rehm, S. Spontaneous testicular lesions in purpose-bred Beagle dogs. Toxicol Pathol 28, 782-787, 2000.

I would be more inclined to accept the pathologist's proposal that the hypo/aspermatogenesis was a background lesion if:

1. the statistical probability of that 6% incidence occurring 4 times in 3 drug-treated groups was higher
2. if the cases of hypo/aspermatogenesis occurred also in the control groups
3. if clevidipine was not a calcium channel blocker, drugs which appear to have a class effect of interfering with spermatozoa via the calcium ion channels.
4. if there was not a decrease in testicular weight in drug-treated dogs.

Histologic findings at end of treatment period

	saline	lipid	Clevidipine mg/kg		
			6.8	16	66
Epididymus: oligospermia	-	-	-	-	2
Epididymus: fibrosis	-	-	-	-	2
Heart: hemorrhage	-	-	-	1	2
Heart: degeneration +/- or necrosis	-	-	-	-	1
Heart: inflammation	-	-	-	-	2
Testis: hypo/aspermatogenesis	-	-	-	-	2
Testis: degeneration seminiferous epithelium	-	-	-	-	2
Testis: mononuclear cell infiltration-	-	-	-	-	2
Histologic findings at end of recovery period					
Epididymus: oligo/aspermia	-	-	1	1	-
Testis: hypo/aspermatogenesis	-	-	1	1	-
Testis: degeneration seminiferous epithelium	-	-	1	-	-
Testis: tubular hypoplasia	-	-	1	-	-

Summary:

These studies were performed to address specific questions of genotoxicity and reproductive toxicity.

The Ames assay conducted with and without formaldehyde dehydrogenase did not produce the decrease in revertants expected in the sponsor's hypothesis. In one trial with FDH, the number of mean revertants produced by the positive controls decreased with the use of FDH. Formaldehyde was not included as a control. The validity of both the study and the hypothesis is questionable.

The Seg II study in rabbits showed dams affected with dystocia and prolonged parturition, referable to calcium's role in uterine contraction. A NOAEL for this was not identified. There was no apparent increase in fetal anomalies.

The Seg III study in rats was also affected by problems associated with calcium channel blockers. There was a dose-related effect of dystocia and prolonged parturition. As a result there were less than an optimal number (less than current ICH guidelines) of pups for evaluation in the MD and LD groups and no pups at all in the HD group. Dams were clearly dosed to the point of toxicity. Maternal parameters of gestation index, live litter size and live birth index were dose-dependently decreased. Viability of pups on day 4 was dose-dependently decreased. Day 7 viability was unaffected across groups.

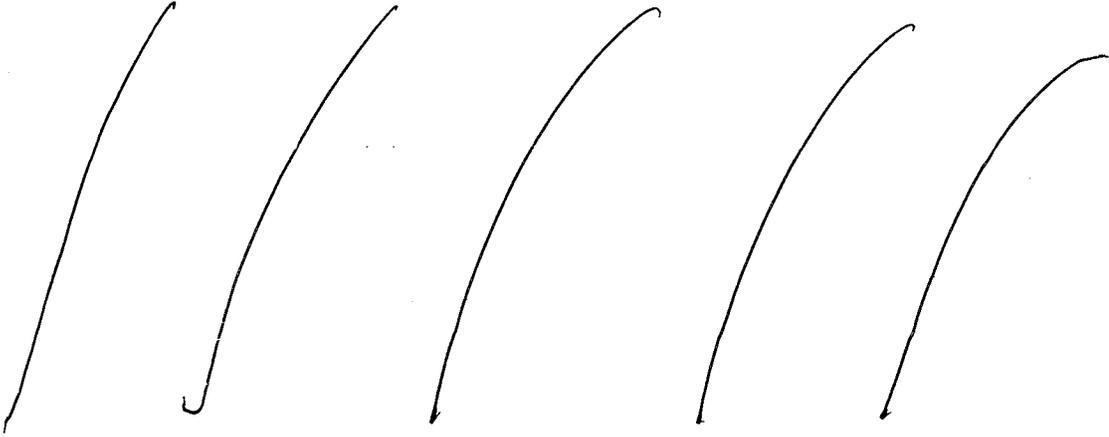
In the assessment of developmental landmarks in the F1 pups, there was a slight, dose-related increase in time to vaginal opening. There was also an apparent trend of dose-related decrease in reproductive performance in the F1 generation. There is no indication that the F1 testes/spermatozoa were assessed.

A 14-day dog study with 28 days of drug-free recovery was used to assess testicular effects. Unfortunately, the sponsor chose to use ejaculated samples for the majority of the evaluation. While the methods section states that histologic evaluation of stage-dependent spermatogenesis was conducted, no summary of the findings and no reference to the findings was located in the report. Aspermatogenesis and hypospermatogenesis were identified in 1LD, 1 MD and 2 HD dogs. The sponsor felt that this was more a result of immaturity rather than drug exposure. This is possible but the reasoning is not entirely convincing. The material presented does little if anything to dispel the impression that clevidipine causes adverse effects upon canine testes.

Reviewer: _____

IND No. _____

The Investigator's Brochure requires the following revisions:



Internal comments: See above.

External comments (to sponsor): A meeting with the sponsor is scheduled for late January. The revisions to the IB can be presented at that time.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

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

/s/

Elizabeth Hausner
1/4/2007 10:46:09 AM
PHARMACOLOGIST
Elizabeth Hausnere

Albert Defelice
1/4/2007 11:58:00 AM
PHARMACOLOGIST

IND 65114

REVIEW AND EVALUATION OF A REPRODUCTIVE TOXICITY STUDY

C.A. Resnick, Ph.D.
DCRDP (HFD-110)

SPONSOR: The Medicines Company

DRUG: Clevelox™ (Clevidipine, H 324/38)

PHARMACOLOGIC CATEGORY: Ca⁺⁺ Channel Blocker

PROPOSED INDICATION: _____

SUBMISSION (serial # 026) DATE: 08 September 2004

CENTER RECEIPT DATE: 09 September 2004

REVIEW COMPLETION DATE: 30 November 2004

RELATED IND: 50261 (AstraZenica) for Clevidipine as iv treatment of _____

BACKGROUND: Clevidipine was developed by Astra Hassle of Molndal, Sweden, and all preclinical work was done by them in the mid-1990s. Clevidipine (0.5 mg/mL) is an emulsion formulated in 20% lipid and is dosed by titration to blood pressure lowering effect. It is indicated in patients _____ thereby limiting the patient population and the duration of dosing _____ for a total duration of a _____. At a 28 July 2004 meeting with the Medicines Company, a number of preclinical issues were discussed. Among those issues was the acceptability of a completed male rat fertility study. On 08 September 2004, as a follow up to that discussion, the undersigned requested (by telephone) that the complete study report be resubmitted to the division. (The report had been previously submitted by Astra but was never reviewed as the Astra IND was inactivated (in early 1998) before the assigned reviewer could complete her review.) Sponsor reports that in a clinical trial in cardiac surgery, 3.2 mcg/kg/min (7 nmol/kg/min) clevidipine demonstrated a therapeutic blood pressure lowering effect in greater than 95% of patients.

H 324/38: Continuous Intravenous Infusion Fertility Study in the Male Rat

Testing Facility: Astra Safety Assessment
Leicestershire, U.K.

Study Number: 96043¹ **Report Number:** 96043-1 **Project Number:** 2011

¹ The male rats were treated with clevidipine for 27 days under study number 96008 (a one month intravenous infusion general toxicology study in male and female rats) before entry into study number 96043.

Study Start Date: 25 July 1996 Study Completion Date: 21 November 1996

GLP Compliance: Statement of compliance with FDA GLP regulations, OECD GLP principles and U.K. Department of Health Compliance programme provided. Quality Assurance Statement also provided.

Test Substance: Clevidipine was supplied by Astra Hassle and formulated by _____ in 20% w/v Intralipid® at concentrations of 1.0, 1.8 and 3.0 mg/mL (batch numbers AH-005, HL-003 and AS-007, respectively). All batches were analyzed and found to be 97% H 324/38. The vehicle, 20% Intralipid® (batch number 84085-51), was obtained from _____ which also supplied Intralipid® (batch number 73172-51) used to flush the high dose cannulae. Sodium Chloride for Intravenous Infusion BP (batch number 22966), was obtained from Astra Charnwood.

Animals: Male Sprague Dawley-derived rats were obtained from _____. They were housed in the Astra Safety Assessment Building under artificial light between 0600 hours and 1800 hours, and in darkness between 1800 hours and 0600 hours (GMT). All animals had free access to tap water and palletized diet. They were allowed a minimum of 11 days to acclimatize before surgery for cannula insertion into the right femoral vein. After insertion of the cannula, the animals were fitted with jackets to protect the implanted cannula and to anchor the skin button/spring tether system. Upon recovery from anesthesia, the animals were continuously infused with saline for at least 5 days, after which they were allocated to dose groups. The animals were approximately 11 to 12 weeks old with body weights between 333 and 465 g, on the first day of dosing. Following 27 days of dosing, the surviving rats (about 15-16 weeks of age) were mated with untreated females (about 13 weeks of age) which were in pro-oestrus. If the pairing was unsuccessful, the male was paired with another naïve female in pro-oestrus during the subsequent night. The males were continuously infused throughout the mating period. The females were sacrificed on day 13 of pregnancy to assess pre and post implantation losses.

Mode of Administration of Test Agent: Continuous intravenous infusion (24 hours per day) at a volume rate of 0.92 mL/kg/hr. Three groups of 10 male rats were dosed with clevidipine at doses of 50, 85 and 145 µmol/kg/day (equivalent to 23, 39 and 66 mg/kg/day) for at least 27 days. Additional groups of 10 males received either the vehicle, 20% Intralipid®, or Sodium Chloride for Intravenous Injection (saline) at a rate of 0.92 mL/kg/hr and served as controls. Note that the study design table that appears below (provided by the sponsor) includes only the number of animals that survived to day 27 (the only animals available for evaluation of mating and fertility).²

**APPEARS THIS WAY
ON ORIGINAL**

² Most of the high dose males were removed from the study between weeks 3 and 4 due to blocked cannulae as a result of compound precipitation.

Study Design

Group	No. of Male Animals	Treatment	Dose Level ($\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$)	Dose Level ($\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$)	No. of Female Animals
1	10	Saline	0	0	12
2	8	Intralipid	0	0	8
3	8	H324/38	50	23	8
4	10	H324/38	85	39	11
1*	10	Saline	0	0	10
5	2	H324/38	145	66	3

a: Concurrent controls for Dose Group 5

Observations/Measurements: All male animals observed at least once daily for signs of ill-health or reactions to treatment (including behavioral changes). Body weights were recorded weekly and food and water consumption were measured continuously for all main study animals. Ophthalmoscopy was performed before commencement of dosing and on all surviving animals after about a month of treatment. The examinations were conducted with an indirect ophthalmoscope and, if needed, a hand-held slit lamp. Blood samples for clinical chemistry and hematology were taken from the tail vein of all surviving animals immediately prior to necropsy. Urinalysis was conducted on urine collected (for 6 hours) from all surviving main study animals on day 28. On days 7 and 28, eight satellite animals from each clevidipine group and eight satellite animals from the vehicle control group were to be bled from the orbital sinus plexus for determination of plasma levels of clevidipine and its major metabolite, H 152/81. Samples from each of these animals were taken at both 9am and 12am. Different animals were bled on day 7 than on day 28. Also, because the high dose males had been removed from the study before the scheduled bleed on day 28, there was no day 28 sampling from those animals (see Results, below). At study termination all animals were killed and subjected to a detailed necropsy, including organ weight measurements. Samples of preputial gland, testis, prostate, epididymis and seminal vesicles (and miscellaneous other tissues) from saline control, vehicle control and animals treated with 145 micromol/kg/day (66 mg/kg/day) were sectioned and stained with H&E. Tissues from other animals were retained in fixative.

APPEARS THIS WAY
ON ORIGINAL

Results

All of the males successfully mated (sperm in vaginal smear), with the exception of a saline control male which was "inadvertently terminated before it was given a second opportunity to mate". The fertility index (successful matings resulting in pregnancy) was 100, 89 and 100% for the low, mid and high dose groups, respectively; all values similar to or exceeding corresponding values for the Intralipid or saline control groups. As clear from the sponsor's tabular summary of implantation data, which follows, there were no effects of treatment (drug or intralipid) on the numbers of implantations, viable embryos or pre- and post-implantation losses. Nor were there effects on weight or morphology of the male reproductive organs.

Summary of Implantation Data

Mean or Range	Dose Group 1	Dose Group 2	Dose Group 3	Dose Group 4	Dose Group 1	Dose Group 5
Number of rats mated	10	8	8	9	9	2
Number of rats pregnant when necropsied	9	7	8	8	9	2
Number of viable litters	9	7	8	8	9	2
Corpora Lutea						
Mean number per rat	17.89	17.14	16.88	18.00	18.11	16.00
Range of individual values	15-21	15-19	16-18	15-20	15-26	16
Implantations						
Mean number per rat	16.33	16.00	14.75	17.13	16.78	16.00
Range of individual values	12-19	13-18	10-17	15-19	14-20	16
Viable Embryos						
Mean number per rat	15.6	15.6	14.3	15.8	15.9	15.5
Range of individual values	9-19	11-18	10-17	14-18	13-19	15-16
Pre-Implantation Loss						
Mean number per rat	1.56	1.14	2.13	0.88	1.33	0.00
Range of individual values	0-5	0-4	0-8	0-2	0-8	0
Mean percentage loss	8.59	6.59	12.27	4.65	6.06	0.00
Range of individual values (%)	0.00-23.81	0.00-23.53	0.00-44.44	0.00-11.11	0.00-30.77	0.00
Post-Implantation Loss						
Mean number per rat	0.78	0.43	0.50	1.38	0.89	0.50
Range of individual values	0-3	0-2	0-2	0-5	0-2	0-1
Mean percentage loss	5.56	3.15	3.24	7.50	5.22	3.13
Range of individual values (%)	0.00-25.00	0.00-15.38	0.00-13.33	0.00-26.32	0.00-13.33	0.00-6.25

Systemic exposures to clevidipine and its metabolite, H152/81, were generally dose related (highest plasma levels occurred in animals treated with the highest dose level). However, although median levels increased with dose, there was a good deal of overlap for individual values between adjacent dosage levels. Concentrations of the metabolite were less variable and showed a better relationship to the dose of clevidipine. The metabolite concentrations (which are reported as $\mu\text{mol/L}$), are also much higher than the concurrent concentrations of clevidipine (reported as nmol/L). The table which follows was prepared from information contained in the report of study #96008, the one month continuous infusion general toxicity study that was the source of the animals used for the male fertility study.

Blood Concentrations of Clevidipine and H 152/81 in Male Rats (median and range)

Each animal sampled twice, 3 hours apart.

Dose (mg/kg/day)	Sampling Day	n	Clevidipine (nmol/L) 9-10 AM	Clevidipine (nmol/L) 12-1 PM	H152/81 (µmol/L) 9-10 AM	H152/81 (µmol/L) 12-1 PM
23	7	4	36.75 (9.3-52.6)	26.45 (13.2-37.7)	94.6 (75.3-136)	101.45 (83.0-126)
23	28	4	18.45 (5.1-120)	25.1 (8.9-88.2)	94.6 (81.9-110)	93.55 (76.2-109)
39	7	4	72.7 (19.7-84.7)	59.0 (29.6-83.3)	142.5 (134-152)	144.5 (142-150)
39	28	3*	16.2 (<5-50.3)	62.8 (<5-101)	123 (102-140)	137 (103-151)
66	7	4	79.4 (21.3-103)	116.3 (38.0-170)	190 (124-197)	173 (130-204)
66	28	0*	-	-	-	-

**Of the satellite animals earmarked for clevidipine and H152/81 blood level determinations on day 28, 1 of 4 in the 39 mg/kg/day group and 4 of 4 in the 66 mg/kg/day group were removed from the study due to a cannula blockage problem.*

EVALUATION

Because only two high dose (66 mg/kg/day) animals were studied for effects of clevidipine on male fertility, that dose level (which was not associated with adverse findings) will be, more or less, ignored in our evaluation of the results of the study. Although the results give us no cause for concern regarding the potential for clevidipine to adversely affect reproduction, the study was not up to the current ICH standards for evaluating such effects. Specifically, there were no more than 10 males evaluated in any of the clevidipine-treated groups, i.e., less than the minimum number (16-20) recommended by the ICH reproductive toxicity guidance, and the demonstrated safety margin (between the animal NOAEL and the projected human dose level) is extremely narrow. The highest continuous infusion dose that could be adequately evaluated was 39 mg/kg/day, about 8½ times (on a body weight basis) or 1½ time (on a body surface area basis) a human dose of 4.6 mg/kg/day (3.2 mcg/kg/min for 24 hours) which (according to the sponsor) has been found to provide therapeutic blood pressure lowering in greater than 95% of patients.

The results do suggest that, at doses equivalent to the human dose, the intralipid formulation of clevidipine does not affect mating behavior or fertility of the male rat.

RECOMMENDATION

Unless comparisons of systemic exposures in humans and rats result in a much wider safety margin than indicated by the body surface area corrected dosage comparison provided above, this reviewer considers the rat study as providing an inadequate assessment of the potential of Clevidipine to adversely affect human male fertility. (Human PK data was not included or referenced in the current submission.) The sponsor has been made aware of our position, most recently in a 24 November 2004 telephone conversation between this reviewer and Saraswathy V. Nochur, Ph.D., Senior Director, Regulatory Affairs, The Medicines Company.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Charles Resnick
12/3/04 03:10:26 PM
PHARMACOLOGIST

IND # 65114
Submission Serial No 001

Pharmacology/Toxicology Review

Reviewer: P.Gill-Kumar, M.D.
Review dt: Jan 17, 2003

Correspondence dt: Sept 18, 2002
CDER/HFD-110 receipt dt: Sept 19, 2002
Sponsor: The Medicine Co.
Drug: Clevidipine
Formulation: Emulsion in 20% intralipid for i/v use
Pharmacological Class: Ca⁺⁺ channel blocker
Proposed investigational use:

Introduction

This submission contains Pharm/Tox studies that were referenced in the Investigators' Brochure (IB), but had not been submitted to the division. These studies are reviewed below. *Note:* The submission also contains studies that were reviewed under IND 50261 for clevidipine.

In the text below, 's-s' stands for statistically significant, 's-ns' for statistically not significant and 's-rev' for statistical tests done by this reviewer. Results of statistical tests done by the sponsor are mentioned without a qualifier. '↑' and '↓' indicate increase and decrease respectively in the value of a parameter. The genotoxicity studies reviewed below are certified by Astra Sweden as being compliant with the GLP regulations of the agency.

Effect of Intravenous Infusion of H324/38 (Clevidipine) on Gastric Emptying and Small Intestinal Propulsion of a Test Meal in the Rat (female, SD; study # 405; study date, Dec '94; study site, Astra labs in Sweden)

Groups of rats (body weight range, 187-234 g) were administered different doses of clevidipine by a 20 minute i/v infusion. Groups 2-4 (n=8/group) received clevidipine at the rate of 10, 30 and 90 nM/kg/min respectively. The drug formulation was an emulsion in (ethanol + intralipid). Group-1 (control; n=10) received the vehicle; vol/kg/min was the same in all groups. Five minutes after the start of infusion, the animals were given a test meal containing ⁵¹Cr and charcoal, and were sacrificed 15 minutes after the test meal.

Gastric emptying (GE) was calculated as $\left(1 - \frac{S_G}{S_T}\right) \times 100$, where S_G is ⁵¹Cr activity in the stomach and S_T is the total activity administered. Intestinal propulsion was calculated as the

IND # 65114
Submission Serial No 001#

2

distance of charcoal front from the gastric end of small intestines (SI) expressed as % of total SI length.

Results

Table (next page) shows the results. Values are mean \pm SE. Values that are s-s different from the control group are underlined.

**APPEARS THIS WAY
ON ORIGINAL**

Group	Gastric emptying (%)	Charcoal Front (% of length)
Control (n=10)	63.2±4.5	78±3
Group-2 (n=8)	59.8±3.8 (5% ↓)	78±3
Group-3 (n=8)	51.4±4.7 (19% ↓)	67±4 (14% ↓)
Group-4 (n=8)	43.8±6.2* (24% ↓)	57±5*** (27% ↓)

Note: '*', p= 0.021; '***', p= 0.001

As can be seen, there was a dose related inhibition of gastric emptying and propulsive small intestinal movements in groups 3 and 4, but the decrease was s-s only in group-4 (multiple comparisons v control, Bonferroni t-test, SigmaStat; s-rev).

Discussion

The sponsor has stated that 10 nM/kg/min clevidipine reduced mean arterial pressure in spontaneously hypertensive rats (SHRs) by \approx 15%, and that this dose, therefore may be regarded as the therapeutic dose in the rat. From this the sponsor infers that this study shows that clevidipine does not interfere with gastric emptying or intestinal propulsion at the therapeutic dose in the rat. The sponsor has not mentioned whether the animals were conscious or anesthetized. The studies that were submitted with IND 50261 (sponsor, Astra USA) showed that the potency of clevidipine for reduction in mean arterial pressure in normal rats is \approx 1/6th the potency in SHRs, and the potency in conscious rats was \approx 1/12th the potency in anesthetized animals.

The clinical protocol submitted with this IND is for controlling arterial pressure during the perioperative period so that the pressure remains below normal; $-\Delta$ being maintained within pre specified limits by adjusting the rate of drug administration. The study reviewed above is therefore not very relevant to predict the effect of clevidipine on GI motility. Because the drug is very short acting (t1/2, a few minutes), even if there is inhibition of GI movements, clinically it would not matter.

Structural Chromosome Aberrations in Human Lymphocytes Treated with Clevidipine in-vitro

(study # 95126; study report date, Oct '96; study site, Astra Labs in Sweden; drug batch # 300/94; drug purity, 99.6%)

The tests were done with and without metabolic activation; metabolic activator was S9 fraction prepared from the livers of Aroclor 1254 induced male SD rats. The drug was dissolved in dimethyl sulfoxide (DMS); heparinised blood from a healthy donor was used to culture lymphocytes; 2% phytohemagglutinin (PHA) was added to the culture medium to stimulate growth and division of lymphocytes. In the absence of S9, test compounds were added to the culture medium 47 hours after the addition of PHA, and the cultures were exposed to test substances for 21 and 44.5 hours for the first and second harvests respectively; in the presence of S9, exposure to test substances was for 2 hours. Negative control was DMS

IND # 65114

4

Submission Serial No 001#

and positive controls were methyl methane sulphonate (MMS) and cyclophosphamide (CP) in the absence and presence of S9, respectively. 2000 cells/test condition were examined for determining mitotic index (MI), and 200 metaphases/test condition were analyzed for chromosome aberrations. The slides were scored blindly. Chromatid gaps were listed, but not included for scoring abnormal metaphases. According to the sponsor, the highest concentration of clevidipine that was tested was based on the solubility limit.

**APPEARS THIS WAY
ON ORIGINAL**

Results

Tables below show the results.

Test condition	No. of metaphases scored	No. of abnormal metaphases	No of metaphases with multiple aberrations	Mitoses/1000 cells
Without Metabolic Activation				
<i>First Harvest</i>				
Medium Control	200	4	0	32
Solvent Control	200	3	0	31
Clevidipine, 0.08 mM/L	200	2	0	33
Clevidipine, 0.16 mM/L	200	6	0	37
Clevidipine, 0.32 mM/L	200	16** (p=0.0018)	0	79**** (p<0.0001)
MMS , 0.22 mM/L	200	82**** (p<0.00001)	0	36
<i>Second Harvest</i>				
Solvent Control	200	3		16
Clevidipine, 0.16 mM/L	200	8		66**** (p<0.0001)
With Metabolic Activation				
<i>First Harvest</i>				
Solvent Control	200	6	0	43
Clevidipine, 0.16 mM/L	200	12	0	35
Clevidipine, 0.32 mM/L	200	54**** (p<0.00001)	0	25
Clevidipine, 0.40 mM/L	200	80**** (p<0.00001)	0	25
CP, 0.06 mM/L	200	42**** (p<0.00001)	0	27
<i>Second Harvest</i>				
Solvent Control	200	4	0	36
Clevidipine, 0.40 mM/L	200	13* (p=0.02)	1	41

Note: Abnormal metaphase values for solvent controls and those that are s-s increased v solvent controls are bolded. In the case of MI, solvent control values and values ≤ 50% of solvent control or s-s increased v solvent control are bolded. The statistical tests done were Fishers/chisquare (s-rev).

- Clevidipine was a clastogen with and without metabolic activation. Without metabolic activation the MI was s-s increased v solvent control.
- There is no tabulation of aneuploidy. However, the sponsor has stated that 9 and 14 polyploidal cells were seen at the two highest clevidipine concentrations with metabolic activation. These incidences are s-s (p=0.0018 and p< 0.0001 respectively, Fishers' exact test, s-rev).

Comments: The sponsor states that during degradation of clevidipine _____ in vivo), equimolar amounts of H192/38 and formaldehyde are formed, and that formaldehyde is a known clastogen.

To determine whether the clastogenicity of clevidipine is attributable entirely to formaldehyde, the test was repeated in the presence of formaldehyde dehydrogenase (FDH), which converts formaldehyde to formic acid. The cells were harvested at 67-68 hours (time of first harvest in the test above). The results of the test in the presence of FDH are shown in the table on the next page.

Test condition	No. of metaphases scored	No. of abnormal metaphases	No of metaphases with multiple aberrations	Mitoses/1000 cells
Without Metabolic Activation				
Medium Control	200	2	0	22
Solvent Control+FDH	200	3	0	23
Clevidipine, 0.1 mM/L+FDH	200	2	0	19
Clevidipine, 0.2 mM/L+FDH	200	2	0	42** (p=0.011)
Clevidipine, 0.3 mM/L+FDH	200	4	0	111**** (p<0.0001)
MMS , 0.22 mM/L	200	35**** (p<0.0001)	0	30
With Metabolic Activation				
Solvent Control+FDH	200	0	0	40
Clevidipine, 0.1 mM/L+FDH	200	3	0	28
Clevidipine, 0.3 mM/L+FDH	200	4 (p=0.062)	0	29
Clevidipine, 0.4 mM/L+FDH	200	2	0	16
CP, 0.03 mM/L	200	51**** (p<0.0001)	4 (p=0.062)	20

Note: Abnormal metaphase values for solvent controls and those that are s-s increased v solvent controls are bolded. In the case of MI, solvent control values and values ≤ 50% of solvent control or s-s increased v solvent control are bolded. The statistical tests done were Fishers/chisquare (s-rev).

In the presence of FDH, Clevidipine was not a clastogen. In the presence of metabolic activation, MI at the highest clevidipine dose was < 50% of the negative control value. Therefore, in this test condition, high enough concentrations of clevidipine were used. In the absence of metabolic activation, MI was increased at clevidipine concentrations ≥ 0.2 mM/L. This was also the case in the test done without the addition of FDH.

Discussion

Clevidipine clastogenicity can only be attributed to formaldehyde if FDH has no effect on metabolism of clevidipine. Astra USA, the sponsor of IND 50261 for clevidipine had stated that they had measured the concentrations of H192/81 in the mouse lymphoma tests in the presence and absence of FDH, and found that FDH did not inhibit the metabolism of clevidipine. In view of this, it is reasonable to conclude that the clastogenic effect seen in this test is attributable to formaldehyde, and clevidipine and its metabolite, H192/81, do not have a clastogenic potential.

To test whether the increase in MI is due to a stimulatory effect of clevidipine on cell division, a separate study (study #96208) was carried out in which DNA synthesis in cultures of human lymphocytes incubated under conditions similar to those used in the present study, was measured. The results of this study showed that clevidipine does not stimulate cell division. The sponsor concludes that the increase in MI is probably due to mitotic arrest, a toxic effect of clevidipine. This seems to be a reasonable inference. Study #96208 is briefly described below.

Study #96208; study date, Oct '96; study site, Astra labs. Lymphocytes from 4 subjects were cultured in the presence of phytohaemagglutinin (PHA); PHA was used to stimulate cell division. For each subject, 6 cultures/test condition were done; 0.08, 0.16, and 0.32 mM/L concentrations of clevidipine were tested (the highest concentration is the same as in the clastogenicity test without metabolic activation); cells were harvested at 72 and 96 hours. *Results:* In lymphocyte cultures from each subject and at both harvest times, there was a s-s decrease in DNA synthesis in cultures exposed to 0.32 and 0.16 mM/L clevidipine.

Mouse Micronucleus Test (study # 95115; study date, Oct '96; study site, Astra labs in Sweden; drug batch # 300/94; purity, 99.6%; male NMRI mice)

10-11 week old male mice weighing 35-45g were used in the study. The drug was dissolved in N,N-dimethylacetamide/water (80/20) and administered i/v. Seven animals/test condition were used; clevidipine doses were 18, 90 and 180 µM/kg (in a preliminary toxicity test, there was mortality at dose levels of 300 and 240 µM/kg); control group received vehicle; methyl methanesulfonate (MMS) 59 µM/ml was the positive control; volume/kg was constant across groups. 7/group from the control and clevidipine groups were sacrificed at 24 and 48 hours; positive control group was sacrificed at 24 hours. After sacrifice, femoral bone marrow slides were prepared for determining the proportion of micronucleated polychromatic erythrocyte (MNPs) and the proportion of polychromatic erythrocytes (PEs). In each slide, 1000 erythrocytes were examined to determine the proportion of PEs, and 2000 PEs were examined to determine the proportion of MNPs. *Note:* The sponsor has not indicated whether the slides were read blind.

Results: Table below shows the results.

Test Condition		No. MNPEs /14000 PEs	% MNPEs (Mean±SE)	% PEs (Mean±SE)
24 hours	Vehicle	29	0.207±0.0668	56.886±3.52
	Clevidipine 18 µM/kg	22	0.157±0.0317	57.643±4.708
	Clevidipine 90 µM/kg	18	0.129±0.0376	53.700±4.252
	Clevidipine 180 µM/kg	23	0.164±0.0180	52.443±5.31
	MMS 590 µM/kg	233*****	1.664±0.182*****	54.371±3.449
48 hours	Vehicle	23	0.164±0.0531	40.171±6.487
	Clevidipine 18 µM/kg	36	0.257±0.0369	40.700±3.87
	Clevidipine 90 µM/kg	37	0.264±0.0594	41.629±4.013
	Clevidipine 180 µM/kg	37	0.264±0.0472	43.843±2.846

Note: MNPE values in vehicle control, the highest value in clevidipine groups (if it exceeds the value in vehicle control) and the positive control value are bolded. '*****', $p < 0.00001$. %PE values in vehicle control, the lowest value in clevidipine groups and the positive control value (if lower than the vehicle control values) are bolded. Statistical tests used were Chisquare test for values in the first column and t-test for values in the other two columns (s-rev).

Clevidipine was not shown to be a clastogen in this test.

Discussion: The highest dose of clevidipine was 75% of the lowest lethal dose, and thus seems appropriate. However, the customary methodology for this test is to sample bone marrow at 24, 48, and 72 hours post dose in vehicle and treatment groups. The sponsor did not sample bone marrow at 72 hours. Therefore, the clastogenic potential of the drug has not been tested adequately.

Recommendations:

- The Mouse micronucleus test should be repeated using 24, 48, and 72 hour harvest times for the vehicle and the clevidipine groups. If a clevidipine dose of 200 $\mu\text{M}/\text{kg}$ does not produce mortality, then 200, 100, and 20 $\mu\text{M}/\text{kg}$ doses of clevidipine should be used, otherwise the test should be repeated using the doses used in study # 95115.
- In the clinical studies to be conducted, serum chemistry should include determination of plasma levels of formaldehyde before the start of treatment, at end of treatment and at one or two suitable time points after the end of treatment. The reasons for this recommendation are that a) toxicity of methanol is believed to be due to formaldehyde formed during methanol metabolism and b) results of genotoxicity tests show that genotoxicity of clevidipine is due to the formaldehyde formed during metabolism of the drug. Therefore, it will be useful to know the pharmacokinetics of formaldehyde formed during treatment with clevidipine.

Pritam Gill-Kumar, M.D.

cc: HFD 110/Original IND
HFD 110/CSO

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

/s/

Pritam Gill-Kumar
1/31/03 04:08:20 PM
PHARMACOLOGIST

Charles Resnick
1/31/03 04:15:45 PM
PHARMACOLOGIST

IND # 65114
Submission Serial No 000

Pharmacology/Toxicology Review

Reviewer: P.Gill-Kumar, M.D.
Review dt: July 19, 2002

Correspondence dt: June 26, 2002
CDER receipt dt: June 27, 2002
Reviewer receipt dt: July 2, 2002
Sponsor: The Medicines Co, Cambridge MA
Drug: Clevidipine
Molecular Formula: $C_{22}H_{23}Cl_2NO_6$
Molecular wt: 456.3
Formulation: 0.5 mg/ml emulsion in 20% lipid (soybean oil and egg phospholipids) for i/v administration
Pharmacological Class: Ca^{++} channel blocker
Proposed investigational use: / / / /

Introduction

Astra USA had submitted IND 50261 for this drug in 1996 for _____ y. This IND is in an inactive status as per the sponsor's request sometime in Jan 98. The sponsor had originally stated that the purpose of the protocol was for reduction of perioperative hypertension. Later in a meeting, it was stated that the standard of care in these cases is to keep arterial pressure within a window which is lower than normal arterial pressure and _____

The Medicine Co (TMC), the sponsor of IND 65114, has submitted a letter from AstraZeneca authorizing the agency to refer to IND 50261 in support of the present IND. In view of this, the Pharmacology/Toxicology review of IND 50261 is applicable to this IND.

Clinical protocol submitted with this IND

The protocol submitted with this IND is for a phase II randomized double blind active control (nitroglycerin) trial. Patients scheduled for elective CABG surgery will be randomized to receive i/v nitroglycerin or clevidipine. The drugs will be titrated as required to achieve predefined mean arterial pressure (MAP). Maximum rate of clevidipine administration will be $\leq 8\mu\text{g}/\text{kg}/\text{min}$. Clevidipine up to the maximum rate proposed in this trial has been used in a clinical study conducted under IND 50261.

The only safety concern is that the sponsor has not stated the maximum amount of intralipid that could be administered in one day to a patient. The intralipid package insert states that intralipid more than 500ml should not be administered on the first day. I had brought this to the attention of Dr. Stockbridge at the safety meeting held on 7/16/02.

**APPEARS THIS WAY
ON ORIGINAL**

I had pointed out that:

- As per protocol TMC-CLV-02-01 p1, a 70 kg patient getting the maximum possible doses (8µg/kg/min for 2 hours, and 4.3 µg/kg/min for 16 hours), would receive ≈ 713 ml 20% lipid in 18 hours. The maximum 24 hours infusion of intralipid (according to its package insert) should not exceed 500 ml on the first day.

On p31 of the protocol it is stated that the intralipid recommendation is that the rate should not exceed 1.6 ml/min. But there is no mention that more than 500ml in 24 hours should not be given. It is important to mention this restriction in the protocol.

In view of the above, the sponsor may want to consider a 1 mg/ml formulation. If this formulation were used, a patient requiring the maximum dose would only receive 350 ml lipid.

- P29: According to the protocol, patients randomized to nitroglycerin will also receive intralipid in order to preserve blinding. This may mask any adverse effects due to lipid in the clevidipine group. More important, patients who are not randomized to clevidipine would unnecessarily receive intralipid and might incur some risk due to i/v intralipid administration. The sponsor may be asked to devise a method to protect the blind without having to administer intralipid to patients randomized to nitroglycerin.

Recommended division action

The sponsor should be requested to submit full reports of the following studies, which are referenced in the Investigator's brochure (IB), submitted with this IND.

- General pharmacology studies referenced on pp 18-27 of IB.
 - The following mutagenicity studies referenced on pp 36-37 of IB: a) Chromosome aberration assay in human lymphocytes. b) Lymphocyte transformation test. c) Mouse micronucleus test.
- These studies most probably were not submitted with IND 50,261 by the sponsor.

Pritam Gill-Kumar, M.D.

cc:HFD 110/Original IND
HFD 110/CSO

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

/s/

Pritam Gill-Kumar
7/23/02 12:38:40 PM
PHARMACOLOGIST

Charles Resnick
7/23/02 03:23:30 PM
PHARMACOLOGIST

Drug had previously been investigated for same indication by
another sponsor. That IND was inactivated. New sponsor
was given right of reference to information in
the inactivated IND. New clinical protocol reviewed.