CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-156

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: May 13, 2008

FROM: Abraham Karkowsky, M.D., Ph.D., Team Leader, Division of Cardiovascular and Renal Products HFD-110

TO: Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products HFD-110

SUBJECT: Approvable recommendation for Cleviprex® (clevidipine butyrate; NDA 22-156, The Medicines Company).

This memo supports the approvable recommendation for Cleviprex® (clevidipine butyrate) as a therapy to [redacted] decrease blood pressure when oral treatment is not an option. Since clevidipine's concentrations rapidly change during an infusion, and its effects are intimately related to its concentration, the onset and offset of clevidipine's effects can be readily managed by judicious titration of the drug. Although the sponsor studied clevidipine in the setting of cardiac surgery; either pre-, post- or throughout the surgery, compared to other after load vasodilators, the sponsor did not demonstrate a clinical benefit or harm of clevidipine relative to the positive comparators.

Complete approval for clevidipine is dependant on qualifying three degradants that structurally [redacted] Should these degradants demonstrate genotoxicity, the specifications for their limits would be substantially lower than the sponsor currently proposes. Establishing an expiration dates for the Cleviprex formulation, without knowing what specifications to assign to these degradants, is not yet possible. In addition to the three degradants, there are two in-process related impurities, [redacted] hat are potential genotoxins. The specifications of [redacted] for [redacted] and [redacted] for [redacted] also need tightening.

Other chemistry related issues transmitted to the holder of the DMF holders [redacted] and [redacted] on 25 February 2008. Most of the deficiencies for the drug substance relate to setting specifications for [redacted] impurities and degradants. For the drug product the deficiencies also relate to setting specifications for impurities and degradants. Additional stability data for the initial commercial batches as well as [redacted] is still pending [redacted] Labeling and packaging comments, particularly with respect to the storage of clevidipine was transmitted to the sponsor.

The microbiologist suggests a four hour allowable time limit from the time the vial septum is punctured till the drug may become contaminated. This limit would require even drug that is currently being infused be changed after four hours.

Clevidipine was positive in the Ames test only when incubated with S9 microsomal fraction for the following strains: TA98, TA100 and TA102.The co-incubation of clevidipine in the presence of formaldehyde dehydrogenase abolished the revertant potential in one of the three positive strains, shifted the dose needed to see revertants by a 2-3 fold factor higher concentration in one strain and essentially did not alter the revertant frequency in the third. Of note, no carcinogenicity studies were carried out for clevidipine.

As a consequence of its degradation, clevidipine generates formaldehyde. Formaldehyde is a probable carcinogen based both on animal studies and human exposures. There is substantial evidence that in mice, at doses of formaldehyde in ambient air greater than 10 ppm, nasopharyngeal tumors are observed. Epidemiologic data in humans exposed to workplace formaldehyde suggests there is human risk to the development of nasopharyngeal neoplastic changes. Whether there are risks to humans for tumors at sites other than respiratory sites appears to be uncertain[1].

Formaldehyde is a naturally occurring substance, generated endogenously (through the metabolism of glycine, methionine, choline and serine) as well as being absorbed through exposure in air and through ingestion of foodstuffs. It is pivotal in supplying one carbon sources that enter the nucleic acid pool. Our pharmacologist argues that the input rate of clevidipine and consequently the rate of input of formaldehyde are substantially less than the endogenously generated formaldehyde turnover rate. They also argue that formaldehyde is water soluble and should rapidly be distributed uniformly through the body's water-space.

However, a ^{14}C-tracer study in which rats were given a single intravenous bolus (5 mg/kg - a rather high bolus dose but much less than the maximal exposure for humans) with the ^{14}C-tracer of clevidipine labeled at the carbon that ultimately generates formaldehyde, demonstrated a fairly rapid and broad distribution of the label. Some tissues demonstrated a log greater concentration of label than was measured in blood or plasma. Some of these tissues are rapidly proliferating (myeloid tissue) and some are not particularly high in their proliferation rate (pancreas). The underlying assumptions of a rapid degradation of clevidipine and a uniform distribution of formaldehyde (and therefore, the risk to any tissue) are not entirely consistent with this study.

The most convincing rationale in my mind to minimize the carcinogenic potential of clevidipine is more related to the short term exposure to clevidipine (and therefore minimal risk). There are also precedents of other currently approved drugs, some for long-term use, that generate formaldehyde (both pharmacologists reviews note the precedent of already approved drugs that generate formaldehyde). Not all such drugs

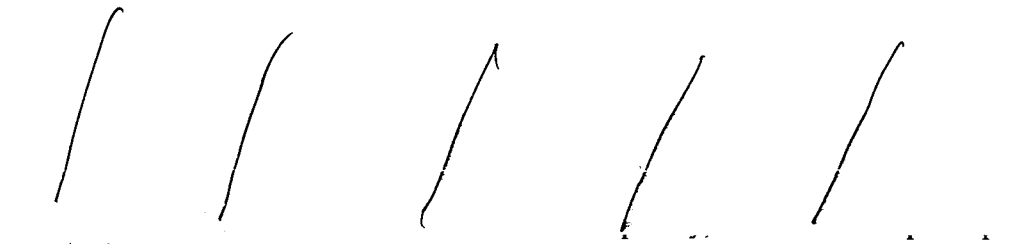
[1] See Heck Hd'A, and Casanova M, " The implausibility of leukemia induction by formaldehyde a critical review of the biological evidence of distant-site toxicity", 2004, Regulator Toxicol and Pharmacol, 40; 92-106.

which generate formaldehyde are carcinogenic in animal studies. Based on the short-term use and inconsistent demonstration of carcinogenicity (despite usually positive mutagenicity tests), the risk for clevidipine appears to be tolerable.

With respect to the dosing instruction of clevidipine, the sponsor recommended a fairly aggressive dose titration regimen, with initial doubling of infusion rates at 90 second intervals [redacted] The sponsor's proposed dosing regimen is fairly aggressive and the scheme will likely result in an overshoot of the goal blood pressure. When the dose is then reduced, the subject would likely have diminished response and the infusion rate would once again need an increase.

If the physician closely monitors blood pressure and modifies the aggressive titration scheme, as the patient's blood pressure approaches a predefined goal, the degree of overshoot and the number of oscillations around goal could be minimized. The most appropriate dosing instructions would, therefore, need to allow for early rapid titration during constant blood pressure and heart rate monitoring, and markedly less aggressive dosing increases and longer waits for further upward titrations as the blood pressure approaches goal.

It is pretty obvious that the sponsor wishes to market Clevidipine [redacted]



[redacted] . I have tried to cut out [redacted] from the package insert.

I am somewhat ambivalent about recommending pediatric studies. As of now, only one drug, fenoldopam, has dosing instructions appropriate for control of blood pressure in children. The magnitude of its effect, however, is modest and the persistence of fenoldopam's effect in children as noted in the current label is limited to the 4 hours for which blood pressure data is available. As such, the study of clevidipine in pediatric population, despite the risk attendant to any exposure to formaldehyde, may be acceptable.

This memo is based on the already completed reviews for the following disciples. There is little information that is present in this memo that is not adequately described by the previous reviewers.

- Chemistry review by Monica D. Cooper, Ph.D. (ONDQA Pre-Marketing Assessment) and Ted Chang Ph.D. (ONDQA Pre-Marketing Assessment and Manufacturing Science Division) dated March 5, 2007.

- Memo by Supervisory Pharmacologist, by Albert DeFelice Ph.D., dated 15 March 2008.
- Pharmacometrics review by Christopher W. Tornoe, Ph.D., dated 30 November 2007.
- Division of Medication Errors and Technical Support memo from Felicia Duffy, RN, safety evaluator dated 20 December 2007.
- Pharmacology-Toxicology Review by E. A. Hausner, D.V.M. dated 28 January 2008.
- DDMAC consult by Lisa Hubbard, R.Ph., dated 17 march 2008.
- DSI memo from Sharon Gerson, Pharm.D., dated 21 November 2007.
- Joint medical and statistical review by B. Nhi Beasley, Pharm.D., and John Lawrence, Ph.D, dated 7 March 2008.
- Microbiology review by Robert J. Mello, Ph.D., dated 29 April 2008.

Housekeeping issues:

DMETS considered the name of Cleviprex® as acceptable. Comments concerning the packaging and labeling from DMETS are summarized at the end of this memo. DDMAC suggested modifications of the tone and content of the package insert. Their recommendations will be considered in the editing of the label.

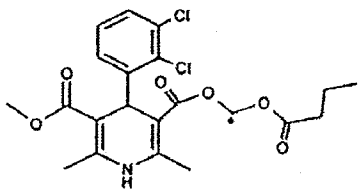
Two sites were inspected by DSI, one site from the study with the acronym ESCAPE -1 and the second from the study with the acronym ESCAPE -2. The auditor considered the data from both sites as credible. Financial disclosures were reviewed in the clinical review and there does not appear to be any concern regarding the integrity of the data.

The EA assessment, contained within the chemistry review was found acceptable. Inspections of the manufacturing site were completed and the Establishment Evaluation Report was acceptable

Chemistry (largely excerpted from the ONDQA review):

The structure of Clevidipine is below. The carbon labeled with an asterisk is the site that ultimately forms formaldehyde and was the site labeled in the ^{14}C-tracer study in rats. Specific information regarding clevidipine is also shown below:

Figure 1: Structure and name of clevidipine butyrate



Clevidipine

* designates ^{14}C radiolabel position

Chemical Names: Butyroxymethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

4-(2',3'-Dichlorophenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid, 3-butyryloxymethyl ester 5-methyl ester

US Adopted Name (USAN): clevidipine butyrate
International Non-proprietary Name (INN): clevidipine
Laboratory Codes: 2930.D and H324/38

Formula $C_{21}H_{23}Cl_2NO_6$
MW 456.3

-Hc

Clevidipine butyrate is a racemic mixture of the dihydropyridine calcium channel blocker shown above. Due its minimal solubility in water, the drug product is formulated as an oil-in-water emulsion containing 0.5 mg/ml. The product is manufactured by

[redacted] The final product is apparently [redacted] The product is stored in the cold (2-8° C) in clear vials but protected from light by its packaging.

The emulsion form of clevidipine is incompatible with certain drugs. Clevidipine should be administered without further dilution. The drug is usually administered by an appropriate pump through a T-joint connection with carrier fluid that may contain one of several commonly used infusates. It should not be administered concomitantly with infusions of other active drugs since the emulsion in unstable when in contact with some active drugs. In the absence of a fuller understanding of the mechanisms that provoke the instability, the co-administration of clevidipine with other active drugs should be avoided.

The chemistry reviewers considered the application as approvable. The review consists of two DMFs # [redacted] for the manufacturing of the drug substance and # [redacted] for the drug product.

The degradation pathway for clevidipine, as adapted from the QA review is shown below. Three of the degradants ([redacted] are not metabolites and therefore, were not qualified as a consequence of the genotoxic screens. Because of their structure [redacted]) they give alerts as potential genotoxins. The limits set by the sponsor for acceptability include a concentration of [redacted] That limit would exceed the acceptable threshold values, as recommended by the EMEA's threshold of Toxicological concern for potential genotoxin substances, by [redacted] Without qualifying these impurities for their genotoxic potential, the appropriate limits for these impurities cannot yet be set and an appropriate expiration date cannot yet be proposed.

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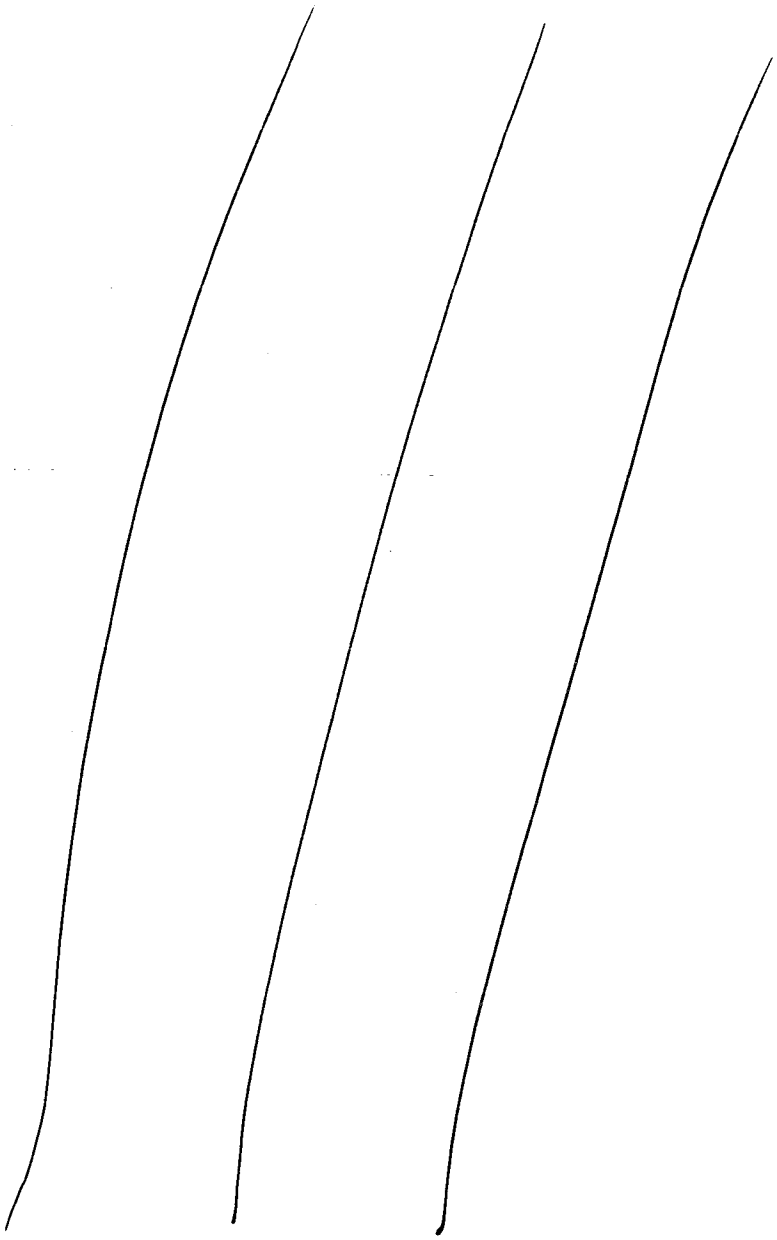
Figure 2: Pathway of clevidipine degradation

Clevidipine Butyrate Degradation Pathway



Additional comments from our ONDA quality assessment reviewer relating to the Drug substance and Drug product are appended at the end or this review. There are also comments that were previously submitted to the DMF holders that contain comments for clarification should also be addressed prior to approval.

Pharmacology (largely excerpted from the Pharmacology reviews):

Clevidipine consists of a racemic mixture containing both R- and S- isomers. Both isomers have calcium channel blockade activity and likely contribute to the observed blood pressure effect. Both of the isomers of clevidipine have approximately the same kinetic properties. The major metabolite of clevidipine (H1) has no antihypertensive activity. Whether the metabolite has other activities is unknown.

Reproductive toxicology:

The effects of clevidipine on reproductive toxicology include dystocia, delayed parturition and impaired male fertility. These outcomes appear to be typical of other calcium channel blockers. Also noted by the Toxicology reviewer were the presence of pseudo-pregnancies and atypical estrous cycles in the clevidipine treated animals. These observations, however, are unique to clevidipine and are not apparently a class effect. The only fetal abnormality that was dose-related was an increase in renal pelvic cavitation.

Genotoxicity:

Since the drug is intended for short durations, carcinogenicity studies were not required and none were performed. Any risk of carcinogenic potential therefore rests on the results of the ability of the drug to provoke mutagenicity and clastogenicity in model systems.

Clevidipine was positive in the Ames test for the strains TA98, TA100 and TA102 only in conjunction with S9-activation. Although this crude fraction is usually added for its mixed-function oxidase activity, it is likely that here the S9 fraction demonstrates esterase activity and its action on clevidipine generated the inactive metabolite H1 as well as formaldehyde. When formaldehyde dehydrogenase is also added to the mixture of clevidipine and S9-fraction, the incidence of revertants did not change with the TA98 strain. For the TA100 strain the incidence of revertants totally reversed and for the TA 102 strain, the incidence of revertants was still significant but the clevidipine concentrations needed to generate these revertants was shifted to about 3 fold higher clevidipine concentrations for similar effects. Since the formaldehyde dehydrogenase is added externally, it is quite feasible that its action in mitigating revertants is dependent on whether formaldehyde is generated in the incubation medium or intracellularly.

Table 1: Revert ants of Strains TA98, TA100 and TA102 with S-9 fraction and with and without formaldehyde dehdrogenase:

	Strain TA98			Strain TA100			Strain TA102	
	w/o FDH	+ FDH		w/o FDH	+ FDH		w/o FDH	+ FDH
Conc (µg/ml)			Conc (µg/ml)			Conc (µg/ml)		
89	+1.5	+1.3	28.1	1.3	0.9	50	1.2	1.0
158	+3.5	+2.4	89	2.5	1.1	89	1.5	1.1
281	+4.5	+4.3	158	6.4	0.9	158	2.5	1.1
						281	4.6	1.8
						500	4.7	2.9

FDH is formaldehyde dehydrogenase, Concentration refers to the concentration of clevidipine

Clevidipine was similarly mutagenic in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test with and without S9 activation. In at least one study, clevidipine, in conjunction with S9 activation in the presence of formaldehyde dehydrogenase, did not increase the frequency of mutants in the mouse lymphoma cell assay in excess of that of the control.

The mouse micronucleus assay was negative. This result is somewhat comforting given the accumulation in ^{14}C-label in myeloid tissue.

Formaldehyde is a metabolite of clevidipine and a known carcinogen in rats when administered by inhalation at concentrations in the ambient air of > 10 ppm. The site of neoplastic changes is related to the site of contact, that is, the respiratory tree in these rodents. In humans, based on occupational exposure, formaldehyde is also a carcinogen of the upper respiratory tract. It is unclear if formaldehyde induces tumors at sites distal to point of its entry. The suggestion has been made that there is an increase in myeloid tumors in conjunction with patients exposed in industrial situations to ambient levels of formaldehyde. As far as I can tell the issue is as yet to be resolved. Both on theoretical basis and when tested by systemic exposure (oral ingestion, not by inhalation), the signals of carcinogenic potential of formaldehyde (or formalin) are at best inconsistent to negative. To the extent that formaldehyde is cleared after oral ingestion by pre-systemic mechanisms, the exposure to this drug systemically may or may not allow for sufficient risk to provoke neoplastic changes

The analysis of the risk of the generation of formaldehyde from clevidipine is complicated by the fact that formaldehyde is a naturally occurring substance, generated endogenously (through the metabolism of glycine, methionine, choline and serine) as well as absorbed through exposure in air and ingestion of foodstuffs. Dr. DeFelice sites published arguments that, given the rapid degradation of formaldehyde, the risk attendant to the infusion of clevidipine is minor. The underlying assumptions include the rapid degradation of clevidipine to formaldehyde (and the inactive moiety H1). Further assumptions are based on the rate of input divided by the rate of clearance of clevidipine (assumed to be all hydrolysis with the generation of formaldehyde) would yield concentrations of formaldehyde or approximately 400 nM, far below the endogenous levels of formaldehyde or 67-100 uM.

There is little data to either support or refute the above theoretical calculations. The only data that I saw was the single dose (bolus) of 5 mg/kg to individual rats with tracer labeled ^{14}C–clevidipine, with the label at the site that eventually generates formaldehyde (see Figure 1). The 5 mg/kg dose, assuming a 70kg individual, is at most approximate to a human dose of 350 mg. With scaling factor included, the 5-mg rat dose actually approximates a 58 mg human dose[2]. During the maximum allowable exposure to humans (16 mg/hour x 24 hr/day x3 days) would be approximately 1152 mg exposure. The single dose is less than the single day exposure of clevidipine.

[2] As per Dr. Hausner

The sponsor treated one animal for each time point. Below I have reproduced the data particularly in organs with the highest concentrations of label. It should be noted that the assay looked at radioactivity. Whether the activity was confined to clevidipine, formaldehyde or already cycled into the one-carbon pool is a matter of conjecture.

Table 2: Concentration of radioactivity of clevidipine as µg-equivalents/g tissue after 5 mg/kg single bolus to rats

	Time						
Tissue	0.5 h	1 h	2 hr	4 hr	8 h	24 h	72 h
Blood	1.2	1.4	1.5	1.4	1.1	0.8	0.6
Bone marrow	**11.4**	**13.2**	**12.6**	**12.7**	**14.4**	**9.1**	**3.0**
Spleen	6.7	7.9	8.1	5.7	9.6	5.0	3.0
Kidney	5.6	6.9	4.9	6.5	5.1	4.3	2.6
Liver	8.5	8.2	6.6	7.2	6.4	3.6	2.1
Thyroid	9.7	8.0	7.5	8.7	6.9	5.6	3.9
Pancreas	**12.8**	**12.6**	**15.0**	**10.2**	**3.8**	**1.7**	**1.2**
Myocardium	2.8	2.6	2.3	2.6	2.6	2.6	1.9

What is clear is that the label clearly accumulates in selected tissues with bone marrow and pancreas containing approximately a log unit higher radioactivity than blood. The concentration of label appears fairly rapidly but does not decline at a rate consistent either with the terminal half-life of clevidipine or with the half-life of formaldehyde. It is possible that this radioactivity defines the amount of clevidipine that entered the C1 pool, but the accumulation appears quite rapid and appears in rapidly proliferating tissue (bone marrow) and tissues not rapidly proliferating (pancreas). It should be noted that a concentration of 15 µg equivalent/gram tissue in pancreas is approximately equivalent to a concentration of 32 µM[3]. This concentration is approximately the concentration of formaldehyde purported to be in tissues.

I am not overwhelmingly convinced that the generation of formaldehyde is a non-issue.

I am more convinced by the short nature of the infusion as well as the precedent of other approved drugs that also generate formaldehyde that the risk of clevidipine for the intended duration is small. Nevertheless, I think whatever risks exist should be described in labeling,

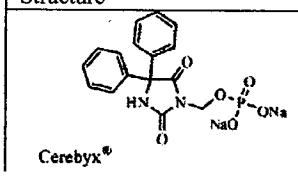
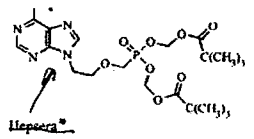
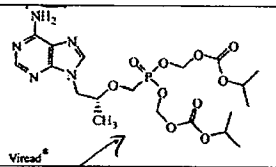
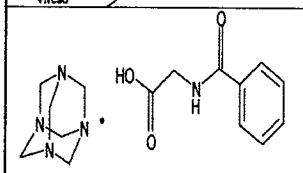
I have collected the formaldehyde generating drugs both approved and those which some data exists. The mutagenic potential of each of these drugs is shown in the Figure 3 as well as whether carcinogenicity is observed. Only Tenofovir disoproxil

[3] 15 µg/g= 15 mg/Kg
=15 mg/L
= approximately 0.032 mM
= 32 uM.

fumarate was positive in a carcinogenicity study with adenomas of the liver as the only finding.

Methenamine hippurate is administered chronically in gram quantities. Each mole of drug generates 6 moles of formaldehyde. Under acid conditions, methenamine is degraded to formaldehyde which is the active antibacterial agent. 10-20% of the administered dose is apparently degraded in the acid stomach environment. There were no signals (there were inadequate signals) in the AERS database (done By Ana Szarfan) for neoplastic changes with methenamine..

Figure 3: Formaldehyde generating drugs, their mutagenicity and carcinogenicity results.

Structure	Name	Use	Mutagen	Carcinogen
 Cerebyx®	Phosphenytoin sodium	Short-term antiepileptic treatment	Structural aberrations in V-79 Chinese hamster lung cells Negative for clastogenicity and Ames study	Not studied
		Apparently in development	Not approved, no data	
	Adefovir dipivoxil	Treatment of chronic hepatitis B	Positive in mouse lymphoma assay with and without activation Induced chromosomal aberrations in in vitro peripheral lymphocytes without metabolic activation	negative
 Viread®	Tenofovir disoproxil fumarate	Treatment of HIV infections	Positive in mouse lymphoma assay. Positive in Ames	Positive for liver adenomas in mice. Negative in rats
	Methenamine hippurate	Treatment of urinary tract infections	Negative	Negative

Biopharmaceutics

Clevidipine is formulated as emulsion in 20% intralipid at a concentration of 0.5 mg/ml for intravenous administration. The kinetic profile of clevidipine can best be described by a multi-compartmental model. After short term infusion, the decay of clevidipine concentration occurs fairly rapid. This portion of the decay curve appears to have a half-life of approximately 1.5 minutes. The processes that decrease clevidipine

concentrations include de-esterification and tissue distribution. When clevidipine is incubated with blood, ex vivo at 37◦C, the concentration of clevidipine decreases with a half-life of approximately 6 minutes. The more rapid decline during in vivo kinetic studies than would be suggested by the half-life for degradation, suggests that redistribution is substantially responsible for the decline in clevidipine's concentrations.

The clearance of clevidipine is only partly dependent on the following covariates: body weight, patient population (hypertension severity), gender and duration of infusion. The covariate effects are modest and the biopharmaceutic reviewers did not recommend alteration of the dose based on these covariates. Since the drug is titratable, based on the above covariates, that recommendation appears reasonable. The concentration and clearance of each of the two optical isomers is similar.

Study TMC-CLV-06-01 was a constant infusion study of clevidipine for 72-hours at four dose levels of clevidipine (2, 4, 8 or 16 mg/hr) or placebo. There was an approximate proportionality in concentrations versus dose, when the infusion rate was in the range of 2 mg/hour to 16 mg/hour. The concentrations seem to demonstrate a diurnal peak effect at about 14 hours after the start of the infusion which diminishes over the next two days.

Clevidipine is largely bound to bound to plasma proteins (> 99.6% in males and females). A mass balance study in humans using tritium-labeled clevidipine (not on the formaldehyde generating site), demonstrated that 83% of the administered label was excreted in the urine and feces after about 72 hours. Of the administered dose, 63-74% was excreted in the urine and 7-22% in feces by the 72 hour time point.

Pharmacokinetic-pharmacodynamic modeling (largely derived from the biometrician review):

StudyTMC-CLV-06-01 was a fixed dose 72-hour continuous infusion study in patients with mild-moderate hypertension. Three patients at each treatment group were treated with a placebo infusion. The study measured both concentrations of clevidipine as well as blood pressure and heart rate effects. At the end of the 72-hour infusion, additional kinetic and dynamic measurements were collected for a total of 4 additional days (96 hours). The data during the infusion was modeled by our pharmacometrician and served as the pivotal source of information in defining the instructions for use for clevidipine. The kinetics during the constant infusion Phase is shown as figure 8A and that for the offset effect is shown as figure 8B. The systolic blood pressure effects during the infusion are shown as Figure 9A and for the offset as Figure 9B. The pharmacokinetic-pharmacodynamic model was fit to an E_{max} model. The E_{max} was a 25% decrease in SBP; the EC_{50} was 7.1 ng/ml. An infusion rate of approximately 10 mg/hr generates this EC_{50} concentration. There was no evidence of an hysteresis effect.

Drug-Drug interactions;

The sponsor did not perform in vivo drug-drug interactions studies with clevidipine. In *in vitro* studies, clevidipine and its major metabolite were inducers of CYP2A4, CYP2C9 and CYP1A2. Of the CYP isozymes tested in vitro, (1A2, 2C9, 2C19,

2D6, 2E1 and 3A4) only CYP 2C9 clevidipine had inhibitory IC_{50} values around the levels anticipated during high dose treatment with clevidipine. The metabolite did not inhibit any of the tested CYP enzymes.

Clinical (Largely derived from the joint clinical-statistical review).
Efficacy

The sponsor supplies more than adequate information to conclude that clevidipine is active in decreasing blood pressure. It is also clear that the blood pressure effect of clevidipine is of substantial magnitude in several populations. Although there is clear evidence for a blood pressure effect of clevidipine, there was no evidence of a clinical benefit, such as a decrease in duration of hospitalization or a decrease in blood loss or need for transfusion. As such, clevidipine is a tool to be used to control or decrease blood pressure. It can't be particularly recommended in any specific circumstance.

Adequate dosing instructions can be constructed that include initial dose and dose escalation regimens. There is sufficient information in the submission that the effect of clevidipine persists during extended infusion durations (3 days). Instructions can be supplied about transitioning patients from clevidipine to other antihypertensive medications.

Safety is somewhat more difficult to describe. Most of the safety data were derived from a peri-operative cardiovascular surgery cohort of clevidipine patients that can be compared to the safety of patients treated with any of three different positive controls (nicardipine, sodium nitroprusside or nitroglycerine). Any modest signal of adverse events is difficult to tease out from the underlying events that occur around cardiac surgery. In addition, the clinical reviewer makes it clear that hypotensive events, which could be treated with decreasing the infusion rate, were not reported as adverse events.

In support of this application, the sponsor submits 19 studies. Of these studies 7 are particularly pertinent for approval and labeling. These studies are described briefly below. The conclusions that are derived are largely based on the review of the biopharmaceutic (Dr Tornoe) and clinical/statistical reviewers (Ms. Beasely/Dr. Lawrence).

- TMV-CLV 03-01 (ESCAPE-1); **E**fficacy **S**tudy of **C**levidipine **A**ssessing its **P**reoperative Antihypertensive **E**ffect in Cardiac Surgery.

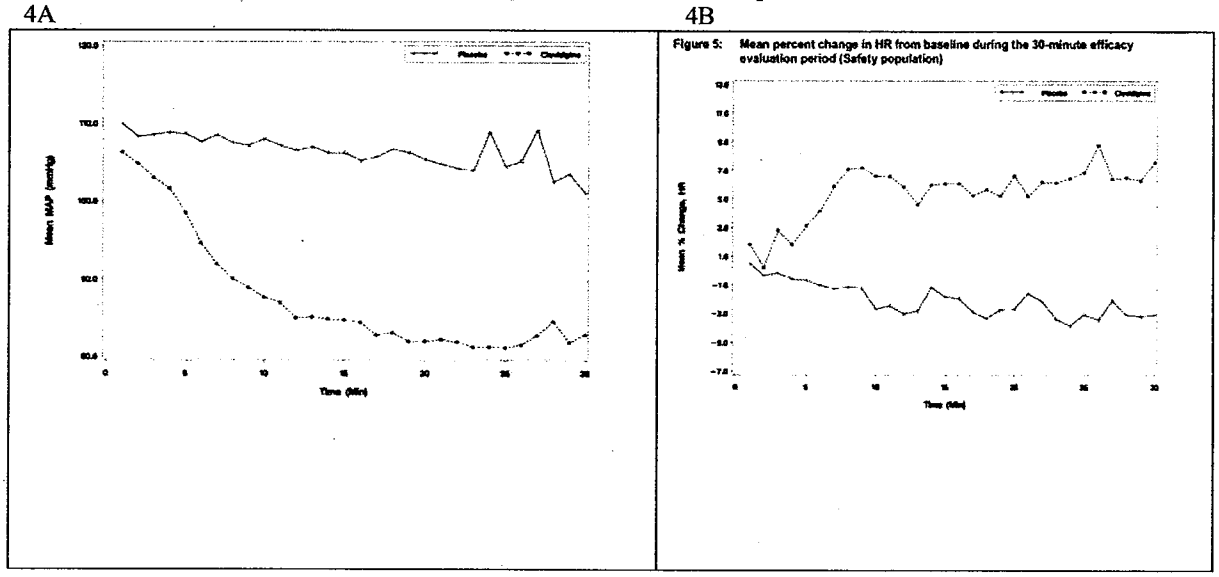
This was a placebo-controlled study that enrolled 104 subjects (53 to clevidipine and 51 to placebo) who either had a history of hypertension or were hypertensive pre-operatively (mean baseline SBP was 179 mm Hg) for one of several cardiovascular operations (CABG and/or valve replacements) and whose blood pressure was to be lowered by at least 15%. These subjects were randomized to placebo or clevidipine treatment. The dosing regimen for clevidipine was 0.4 μg/kg/min the dose could be increased by a factor of two, at 90 second intervals until a dose of 3.2 μg/kg/min was reached. Higher infusion rates, if still needed could be increased at rates of 1.5 μg/kg/min

based on the subjects response. The maximal usable dose is 8.0 μg/kg/min; upward or downward titrations were allowed.

The primary metric was the failure rate of the two treatment groups during the time of interest (30-60 minutes during the infusion or until the start of anesthesia.) Treatment failure consisted of one of three components; 1) bailout for lack of efficacy (failure to have more than a nominal effect on blood pressure), 2) bailout for safety (emergence of an adverse event) or 3) bailout for treatment failure (failure to achieve at least 15% decrease in SBP). Clevidipine was superior to placebo both in the fraction of subjects who responded (4/53 in the placebo versus 43/52 in the clevidipine group) and in the rapidity of systolic blood pressure decrease. Heart rate was correspondingly increased in the clevidipine group. The blood pressure effect and the effect on heart rate are shown below.

Figure 4 A and B- SBP and heart rate during 30 minute treatment period ESCAPE-1

4A 4B



- TMV-CLV-03-02 (ESCAPE-2) Efficacy Study of Clevidipine Assessing its Postoperative Antihypertensive Effect in Cardiac Surgery (ESCAPE-2).

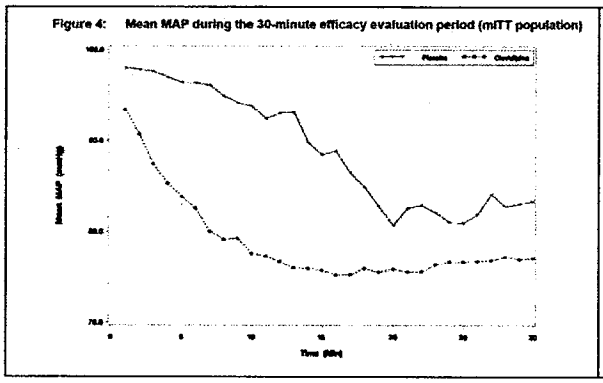
This study was very much similar to ESCAPE-1 except patients were post-operative. The study enrolled 110 patients (61 clevidipine and 49 placebo) who were within four hours of the operative procedure (either CABG or valve surgery), who had a minimum systolic blood pressure of 140 mm Hg and who required a 15% decrease in blood pressure. Those enrolled had a mean systolic blood pressure 148 mm Hg.

Treatment failure consisted of one of three components; 1) bailout for efficacy (failure to have more than a nominal effect on blood pressure), 2) bailout for safety (emergence of an adverse event) or 3) bailout for treatment failure (failure to achieve at

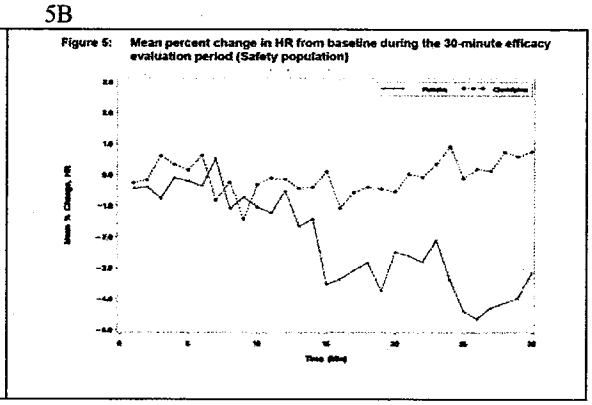
least a15% decrease in SBP). There were substantially fewer subjects in the clevidipine group requiring bailout 5/61 compared to placebo 39/49). The blood pressure and heart rate effects are shown below. Blood pressure and heart rate differed between clevidipine and placebo. During the 30-minute treatment period other antihypertensive medications were precluded.

Figure 5 A and B: Blood pressure (A) and heart rate (B) from ESCAPE-2

5A



5B



- TMC-CLV-06-02. Evaluation of the Effect of Ultrashort Acting Clevidipine in Treatment of Patients with Severe Hypertension (VELOCITY)

This was a baseline-controlled study. The study planned to enroll a minimum of 100 subjects to be treated for a minimum of 18 hours. Subjects were male or female subjects with either baseline SBP > 180 mm Hg and/or DBP > 115 mm Hg. They could have either chronic or acute end-organ dysfunction. After determining eligibility, they were only treated if the blood pressure at the time of treatment was still above the pre-determined eligibility criteria.

Patients were initiated at a dose of 2 mg/hr and this dose was maintained for three minutes. Thereafter, the dose could be doubled at three minute intervals until a predetermined blood pressure was reached. The maximum dose of clevidipine was limited to 32 mg/hr. Subjects were then maintained at this level of blood pressure control by the titration of the dose of clevidipine either upward or downward. If the blood pressure response after the first 30 minutes was inadequate at the highest tolerated clevidipine dose, other mediations were allowed. The duration of treatment was to last at least 18 but less than 96 hours. Patients were transitioned to other antihypertensive medication by the initiation of the new treatment one-hour prior to the discontinuation of clevidipine.

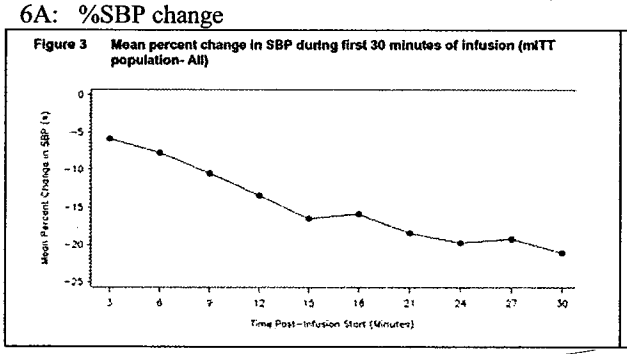
Of the 131 subjects enrolled 117 were eventually treated (14 were excluded because blood pressure was no longer above the entry criteria). Of those enrolled, 77% were African-American and 6% Caucasian. The mean blood pressure at baseline was mean SBP (SD)/mean DBP (SD) was 203 (23)/113 (21). Of the 126 subjects enrolled as the

safety population, 102 had some form of end organ damage. The vast majority of those with end-organ damage appear to have had chronic end-organ damage and the role of this particular event in further organ compromise is not easily teased out.

The baseline subtracted effect on blood pressure and heart rate is shown in Figure 6A. The effects on blood pressure overestimate the true effect because of the potential for a regression to the mean effect. Nevertheless, the rapid and persistent further decrease in blood pressure, after the initial measurement, indicates that further decreased over subsequent dosing changes. Blood pressure and dose were related. Heart rate is shown in Figure 6BFigure 7 is a linear model correlating concentration to blood pressure (the effect is better described by an Emax model) for the VELOCITY and ESCAPE studies.

Figure 6(A) and heart rate (B) VELOCITY study A and B: blood pressure, mean +

6A: %SBP change



6B: heart rate box and whisker plot

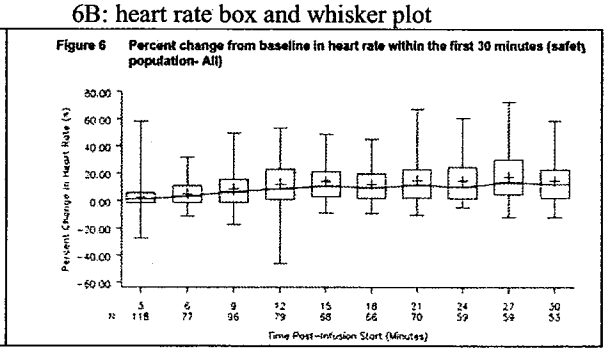


Figure 7: relationship between concentration and SBP effect in the VELOCITY and ESCAPE studies (linear model)

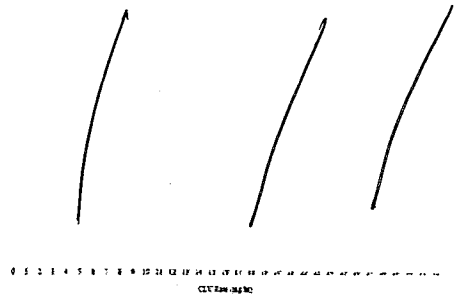


Figure 28. Linear regression of % change of SBP vs. clevidipine infusion by rate (ESCAPE and VELOCITY studies).
(Source: Figure 5.3 in sponsor's integrated summary of efficacy.

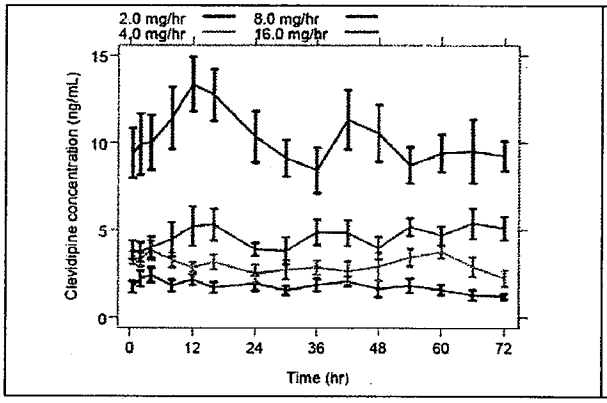
- Study TMC-CLV-06-01. A Randomized, Placebo-Controlled, Single-Blind Study in Patients With Essential Mild to Moderate Hypertension to Evaluate The Pharmacokinetics, Pharmacodynamics and Safety of Clevidipine During and Following Prolonged Continuous Infusion.

This study was a randomized placebo-controlled fixed dose ranging study in subjects with mild to moderate hypertension (SBP $\geq$ 140 < 200 mm Hg; DBP $\geq$ 95 < 115 mm Hg) and who did not have profound tachycardia (HR < 120 bpm). There were four dose cohorts 2, 4, 8 and 16 mg/hr. Within each of the cohorts, 13 patients were to be enrolled of which 3 are to be treated with placebo (intralipid®). Each cohort was started at a dose of 2 mg/hr and titrated to their randomized dose by doubling the dose at 3 minute intervals. A total of 61 subjects were eventually enrolled; 13 to receive placebo, 10 subjects to each of the following dose levels: 2, 4 and 16 mg/hour and 18 subjects to the 8 mg/hr cohort. The infusion duration was for 72 hours. The dose of clevidipine was then discontinued and vital signs measured for an additional 4 days, with frequent monitoring immediately following infusion discontinuation. Blood for pharmacokinetic assessments will be collected at predose and 0.5, 2, 4, 8, 12, 16, 24, 30, 36, 42, 48, 54, 60, 66 and 72 hours during the infusion as well as 2, 4, 8, 12, 20, 30 and 60 minute upon discontinuation of the infusion.

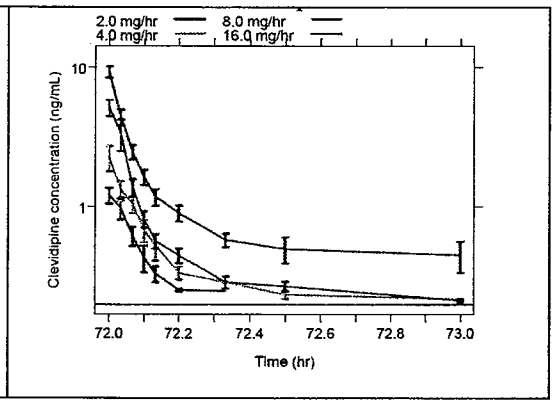
The time course of clevidipine concentration measurements is shown in Figure 8A. Note, there is a diurnal effect, particularly during the first day of treatment. The time course for washout of clevidipine (Figure 8B) is rapid. The washout half-life appears to be 1-2 minutes.

Figure 8: Study 06-01 Concentrations during the 72 hour infusion period (A) and for the hour after the infusion is discontinued (B), Mean $\pm$ SE

8A



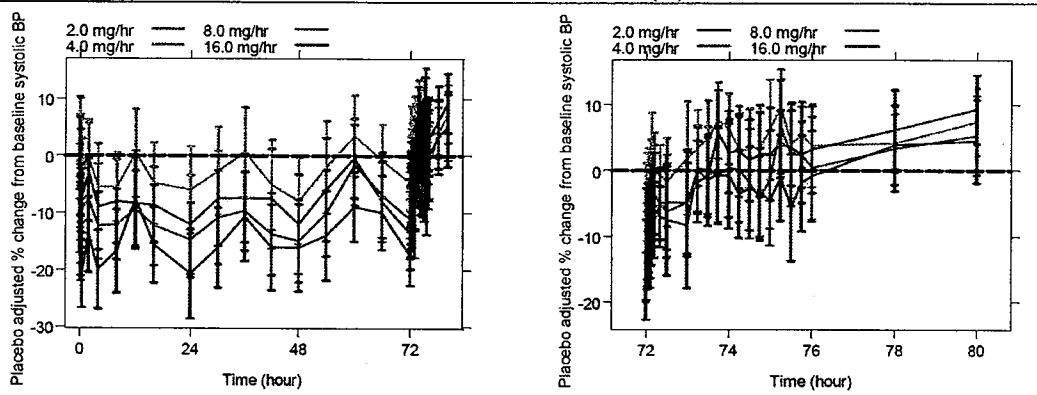
8B



The placebo-subtracted systolic blood pressure decrease during the 72 hour infusion is shown in Figure 9A. For the washout period, the placebo-subtracted data indicate an overshoot of the baseline SBP relative to placebo Figure 9B. Compared to baseline the effect is an approximately 5% overshoot. Compared to placebo, the effect is closer to 9% (approximately 15 mm Hg).

Figure 9: Percent change in SBP during infusion (A) and after discontinuation of infusion (B), mean ± 90% CI.

9 (A) 9(B)



In summary, Clevidipine lowers blood pressure in pre-operative, operative and post-operative settings. Clevidipine also lowers blood pressure in patients with mild to moderate blood pressure as well as severely elevated blood pressure. Based on the lack of a meaningful outcome in the treatment groups, it seems appropriate to approve clevidipine as a tool to decrease blood pressure when oral medication is not feasible or desirable.

Safety:

There were three safety studies that are described briefly below. The studies were open-labeled, multicenter, positive controlled study in patients undergoing bypass surgery and/or valve replacement surgery. These studies were geared to defining safety. Each study employed a different positive control to compare to clevidipine.

- Study TMC-CLV-03-03. Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events (with Nitroglycerin as Active Comparator –ECLIPSE-NTG)
- Study TMC-CLV-03-04. Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events (with Sodium Nitroprusside as Active Comparator –ECLIPSE-SNP)
- Study TMC-CLV-03-05. Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events (with Nicardipine as Active Comparator –ECLIPSE-NIC)

Those enrolled had some need to have their blood pressure controlled either pre-operatively, intra-operatively or post-operatively. Clevidipine was initiated at a dose of 0.4 µg/kg/min with doubling dose every 90 seconds until subjects reached a dose of 3.2 µg/kg/min. Subsequent increases were limited to increase of 1.5 µg/kg/min. The maximum dose was 8.0 µg/kg/min. For each of the positive controls their titration regimen was left to the discretion of the individual investigator. Once goal was achieved, upward and downward titrations of the two infusions were allowed during maintenance

phase to control the blood pressure within the predefined range. At times, the dose of either clevidipine or control could be zero. The reason for the change in infusion rates was not captured on the CRFs. It was therefore, not possible to determine if the reason for titration decreases was related to safety i.e., tachycardia, excessive effect or other reasons.

During the operation, the SBP was to be kept between 65-135 mm Hg and for pre and postoperative periods the control of BP was to be kept at 75-145 mm Hg.

The subjects in each study were randomized in a 1:1 ratio to clevidipine or positive control.

The demographic characteristics of those enrolled in the three studies are shown in Table 3.

Table 3: Demographic characteristics ECLIPSE studies

	Eclipse-NTG		Eclipse-SNP		Eclipse NIC	
Parameter	Clevidipine N=268	Nitroglycerine N=278	Clevidipine N=296	SNP N=283	Clevidipine N=188	Nicardipine N=193
Age (mean ± SD) years	64.6 ± 11	63.9 ± 11	64.2 ± 11	65.3 ±11	66.1 ± 10	66.1 ± 10
Female (%)	20 %	26 %	31%	24%	30%	29%
Caucasian/blacks/Asian (%)	84%/5%/6%	83%/7%/3%	82%/12%/3%	84%/8%/3%	77%/14%/0%	82%/12%/1%
Baseline SBP (mean ± SD) mm Hg	143 ± 23	139 ± 28	142 ±22	142 ± 26	144 ± 19	144 ± 20
Baseline DBP (mean ± SD) mm Hg	72 ± 13	71 ± 15	71 ± 14	71 ± 17	69.2 ± 13	68.4 ± 13
Selected Baseline conditions						
Prior PCI	25%	24%	20%	16%	2%	4%
Stroke	5%	8%	7%	6%	9%	6%
Prior CABG	4%	9%	3%	4%	2%	4%
Hypertension	84%	86%	86%	81%	96%	88%
Diabetes	37%	30%	34%	37%	37%	39%
Atrial Fibrillation	10%	10%	10%	10%	11%	9%
CHF	13%	16%	22%	18%	23%	20%

The majority of patients were male and Caucasian. Systolic blood pressure at baseline was only mildly elevated. The DBP at baseline was clearly within the normal range.

The timing for the initiation of treatment as well as the infusion rates and duration of infusions are shown Table 4:

Table 4: Timing and initial dosing during ECLIPSE studies:

	Eclipse-NTG		Eclipse-SNP		Eclipse NIC	
	Clevidipine	Nitroglycerin	Clevidipine	SNP	Clevidipine	Nicardipine
Preoperative	92 (34%)	119 (43%)	52 (18%)	34 (12%)	0	0
Intra-operative	145 (54%)	132 (48%)	161 (54%)	158 (56%)	0	0
Postoperative	31 (12%)	27 (10%)	83 (28%)	90 (32%)	188 (100%)	193 (100%)
Infusion duration (not including times of no infusion), median	3.35 h	7.93 h	6.7 h	5.4 h	5.6 h	4.6 h
Total infusion time, median	6.4 h	12.0 h	3.9 h	3.2 h	7.1 h	7.9 h
Average Clevidipine dose in mg/hr	3.0		3.2		3.97	
Average clevidipine dose in µg/kg/min	0.57		0.6		0.771	

The duration for treatment and also therefore, for risk of safety signals was longest for the nitroglycerine patients than for clevidipine. In the other two studies the duration of exposure was slightly greater for clevidipine. The dose for clevidipine was modest and was less than the dose that would occur with the first dose titration.

Safety for the pooled Eclipse studies is described later.

Conclusions:

Efficacy:

There is no doubt that clevidipine is a drug capable of decreasing blood pressure. Escape 1 and 2 clearly demonstrate a decrease in blood pressure in pre and post-operative patients relative to placebo. Study 06-01 demonstrates a persistent effect of clevidipine for 72 hours.

Population:

There is adequate information to construct a set of instructions for use in a wide variety of populations. Although the majority of the development program studied clevidipine in a peri-operative setting, the results of study 06-01 studied patients with mild to moderate hypertension and the Velocity study strongly suggests an effect of clevidipine in a severely hypertensive population. It should be noted that no clinical benefit was demonstrated in the entirety of the database. As such, clevidipine seems a useful tool to use on an ad hoc basis to decrease blood pressure.

Dosing:

There is adequate information to define an appropriate set of dosing instructions. Since the drug is titratable, a large potential set of dosing algorithms are possible. The titration instructions need to balance off the need for a rapid (or gentler decline) in blood pressure with the attendant consequence for overshoot of blood pressure effect and risk of provoking tachycardia.

In clinical studies the dosing began at 0.4 μg/kg/min with doubling every 90 seconds until a dose of 3.2 μg/kg/min was reached. If additional blood pressure effect is needed upward titration at an increase in rate of 1.5 μg/kg/min can be considered. The sponsor requested an approximate dose of 2 mg/hr as the initial dose. For lighter patients (e.g. < 60 kg) the initial dose should closer reflect a 1 mg/hour infusion.

Several other alternative algorithms for dosing instructions can be derived from the modeled data. The elements of these instructions would allow for early rapid dose increases but as the blood pressure approaches the goal blood pressure, the dose increments should be decreased and the time between dosing increases should be prolonged. I favor this approach.

With respect to persistence of effect, the drug is still active after 72 hours of infusion. In addition, the offset of the effects of clevidipine, even after prolonged infusions is still rapid. I am somewhat perplexed by the overshoot observed about 8 hours after the cessation of therapy. As of now, the instructions should indicate cautionary language for rebound hypertension for at least 8 hours post infusion. No hysteresis was observed

Drug-Drug interactions:

As noted above, the sponsor did not perform in vivo drug-drug interactions studies with clevidipine. In *in vitro* studies clevidipine and its major metabolite were inducers of CYP2A4, CYP2C9 and CYP1A2. Of the CYP isozymes tested in vitro, only CYP 2C9 was inhibited by clevidipine with IC_{50} values around the levels anticipated during high dose treatment with clevidipine. The metabolite did not inhibit any of the tested CYP enzymes.

Safety:

Most of the studies are small. One study was performed in severely hypertensive patients (the VELOCITY study) but was uncontrolled. The large numbers of adverse events as well as serious adverse events in that study can be attributed to either therapy or the baseline status of the patient.

The most useful studies for defining safety were, therefore, the three studies in the peri-operative cardiovascular surgery population. Each of these studies used a different positive control. For each of the studies the dosing algorithm for clevidipine was as described above. For the positive comparator, the dosing algorithm for the comparator drug (nitroglycerin, sodium nitroprusside or nicardipine) was left to the general practice of the investigator. Safety was assessed during the 30 day post-operative period. Given the large number of events simply related to the surgery, it is difficult to differentiate any signal for the underlying noise of the peri-operative safety.

The sponsor prepared a safety assessment dealing with adverse events and serious adverse events that were timed to within one-hour of the end of the infusion.

The original safety assessment was to demonstrate a statistical benefit of clevidipine, relative to the comparator drugs for the incidence of death, stroke, myocardial infarction and renal dysfunction, during the 30-day post-operation period.

The pooled analysis did not show a statistically significant benefit relative to the proposed outcome.

With respect to comparative safety, there does not appear to be substantial differences between overall Clevidipine and "All" comparators.

Table 5: Serious adverse events pooled ECLIPSE studies (> 4 events either in clevidipine or all comparators)

Event	Clevidipine N=752	Nitroglycerin N=278	Sodium nitroprusside N=283	Nicardipine N=193	All comparators N=753
Patients with at least one AE	30 (4%)	16 (6)	21 (7%)	10 (5%)	47 (6%)
Cardiac disorders	12 (2%)	6 (2%)	5 (2%)	3 (2%)	14 (2%)
Ventricular fibrillation	3 (0.4%)	2 (0.7%)	1 (0.4%)	1 (0.5%)	4 (0.5%)
Respiratory , thoracic or mediastinal disorders	5 (0.7%)	4 (1.4%)	8 (2.8%)	3 (1.6%)	15 (2%)
Mediastinal hemorrhage	1 (0.1%)	1 (0.4%)	3 (1.1%)	0	4 (0.5%)
Nervous system disorders	5 (0.7%)	1 (0.4%)	0	1 (0.5%)	2 (0.3%)
Injury poisoning and procedural complications	4 (0.5%)	3 (1.1%)	3 (1.1%)	2 (1.0%)	8 (1.1%)
Post procedural hemorrhage	4 (0.5%)	3 (1.1%)	2 (0.7%)	2 (1.0%)	7 (0.9%)
Renal and urinary disorders	3 (0.4%)	1 (0.4%)	1 (0.4%)	2 (1.0%)	4 (0.5%)

Table 6: Overall Adverse events > 2% in pooled clevidipine or any treatment

Event	Clevidipine N=752	Nitroglycerin N=278	Sodium nitroprusside N=283	Nicardipine N=193	All comparators N=753
Patient with at least one	170 (23%)	71 (26%)	70 (25%)	22 (11%)	163 (22%)
Injury poisoning and procedural complications	290 (39%)	115 (41%)	105 (37%)	84 (44%)	304 (41%)
Incision site complication	205 (27%)	100 (36%)	29 (21%)	60 (31%)	219 (29%)
Post Procedural pain	60 (8%)	8 (3%)	25 (9%)	22 (11%)	55 (7%)
Post procedural hemorrhage	20 (3%)	5 (2%)	24 (9%)	6 (3%)	35 (5%)
Post Procedural discharge	20 (3%)	4 (1%)	12 (4%)	0	16 (2%)
Cardiac disorders	261 (35%)	86 (31%)	105 (37%)	76 (39%)	267 (35%)
Sinus Tachycardia	103 (14%)	47 (17%)	40 (14%)	34 (18%)	121 (16%)
Atrial fibrillation	37 (5%)	12 (4%)	12 (4%)	6 (3%)	40 (4%)
Ventricular extrasystoles	29 (4%)	8 (3%)	13 (5%)	15 (8%)	36 (5%)
Ventricular tachycardia	24 (3%)	5 (2%)	9 (3%)	6 (3%)	20 (3%)
Right bundle branch block	20 (3%)	5 (2%)	10 (4%)	2 (15)	17 (2%)
Ventricular tachycardia	14 (2%)	5 (2%)	7 (3%)	6 (3%)	18 (2%)
Cardiac failure, congestive	13 (2%)	3 (1%)	0	11 (6%)	14 (2%)
Supraventricular extrasystoles	12 (2%)	1 (< 1%)	3 (1%)	4 (2%)	8 (1%)
Cardiomegaly	9(1%)	4 (1%)	1 (< 1 5)	1 (< 1%)	12 (2%)
Respiratory, thoracic and mediastinal disorders	249 (33%)	89 (32%)	102 (36%)	85 (44%)	276 (37%)
Atelectasis	131 (17%)	62 (22%)	56 (20%)	31 (16%)	149 (20%)
Pleural effusion	47 (6%)	17 (6%)	18 (6%)	22 (11%)	57 (8%)
Breath sounds decreased	28 (4%)	3 (1%)	16 (6%)	11 (6%)	30 (4%)
Pulmonary congestion	19 (3%)	6 (2%)	12 (4%)	2 (1%)	20 (3%)
Rhonchi	19 (3%)	1 (< 1 %)	14 (5%)	15 (8%)	30 (4%)
Pulmonary edema	15 (2%)	13 (5%)	9 (3%)	5 (3%)	28 (4%)
Abnormal chest sound	14 (2%)	3 (1%)	7 (3%)	7 (4%)	17 (2%)

Hypoxia	10 (1%)	3 (1%)	3 (1%)	5 (3%)	11 (2%)
Respiratory failure	9 (1%)	2 (1%)	7 (3%)	5 (3%)	14 (2%)
Cough	8 (1%)	1 (< 1%)	1 (< 1%)	5 (3%)	7 (1%)
Productive cough	7 (1%)	4 (1%)	0	3 (2%)	7 (1%)
Pneumothorax	6 (1%)	5 (2%)	3 (1%)	4 (2%)	12 (2%)
Wheezing	6 (1%)	3 (1%)	1 (< 1%)	8 (4%)	16 (2%)
Restrictive pulmonary disease	1 (<1 %)	7 (3%)	0	0	7 (1%)
Investigations	212 (28%)	70 (25%)	79 (28%)	71 (37%)	220 (29%)
White blood cell count incr	74 (10%)	32 (12%)	22 (8%)	15 (8%)	69 (9%)
Hematocrit decreased	56 (7%)	29 (10%)	19 97%)	10 (5%)	58 (8%)
Hemoglobin decreased	54 (7%)	13 (5%)	26 (9%)	16 (8%)	55 (7%)
Platelet count decreased	45 (6%)	17 (6%)	20 (7%)	3 (2%)	40 (5%)
Red blood cell count decreased	33 (4%)	4 (1%)	15 (5%)	5 (3%)	24 (3%)
Blood glucose increased	31 (4%)	4 (15)	8 (3%)	9 (5%)	21 (3%)
Blood calcium decreased	28 (4%)	2 (1%)	14 (5%)	7 (4%)	23 (3%)
Neutrophil count incr	27 (4%)	1 (< 1%)	11 (4%)	4 (2%)	16 (2%)
Body temperature increased	24 (3%)	7 (3%)	10 (4%)	10 (5%)	27 (4%)
Lymphocyte count decreased	22 (3%)	1 (< 15)	10 (4%)	5 (3%)	16 (2%)
Urine output decreased	14 (2%)	10 (4%)	2 (1%)	4 (2%)	16 (2%)
Blood lactate dehydrogenase incr	11 (2%)	3 (1%)	3 (1%)	7 (4%)	13 (2%)
General disorders and administrative site conditions	145 (19%)	48 (17%)	61 (22%)	75 (40%)	184 (24%)
Anasarca	37 (5%)	2 (1%)	17 (6%)	16 (8%)	35 (5%)
Pyrexia	33 (4%)	10 (4%)	11 (4%)	20 (10%)	41 (5%)
Pain	27 (4%)	18 (7%)	4 (1%)	11 (6%)	33 (4%)
Edema Peripheral	23 (3%)	6 (2%)	7 (3%)	7 (4%)	20 (3%)
Asthenia	17 (2%)	1 (<1%)	7 (3%)	12 (6%)	20 (3%)
Edema	16 (2%)	11 (4%)	5 (2%)	16 (8%)	32 (4%)
Crepitations	7 (2%)	2 (1%)	0	7 (4%)	5 (1%)
Rigors	5 (1%)	4 (1%)	5 (2%)	7 (4%)	16 (2%)
General symptom	1 (< 1%)	1 (< 1%)	2 (1%)	6 (3%)	7 (1%)
Metabolism and nutrition disorders	117 (16%)	38 (14%)	48 (17%)	61 (32%)	147 (20%)
Hyperglycemia	63 (8%)	23 (8%)	22 (8%)	34 (18%)	79 (11%)
Hypokalemia	27 (4%)	10 (4%)	13 (5%)	12 (6%)	35 (5%)
Fluid overload	13 (2%)	6 (2%)	8 (3%)	4 (2%)	18 (2%)
Hypocalcemia	12 (2%)	1 (<1%)	5 (2%)	5 (1%)	11 (2%)
Acidosis	4 (1%)	2 (1%)	2 (1%)	4 (2%)	8 (1%)
Blood and lymphatic system disorders	115 (15%)	47 (17%)	52 (18%)	43 (22%)	142 (19%)
Anemia	85 (11%)	39 (14%)	42 (15%)	30 (16%)	111 (15%)
Leukocytosis	37 (5%)	11 (4%)	10 (4%)	9 (5%)	30 (4%)
Thrombocytopenia	25 (3%)	8 (3%)	10 (4%)	20 (10%)	38 (5%)
Gastrointestinal disorders	98 (13%)	37 (13%)	28 (10%)	30 (16%)	95 (13%)
Nausea	60 (8%)	25 (9%)	11 (4%)	19 (10%)	55 (7%)
Bowell sounds abnormal	27 (4%)	4 (1%)	11 (4%)	6 (3%)	21 (3%)
Vomiting	13 (2%)	6 (2%)	6 (2%)	9 (5%)	21 (3%)
Psychiatric disorders	70 (9%)	17 (6%)	24 (9%)	17 (9%)	58 (8%)
Agitation	35 (5%)	6 (2%)	7 (3%)	10 (5%)	23 (3%)
Anxiety	26 (4%)	7 (3%)	8 (3%)	7 (4%)	22 (3%)
Confusional state	13 (2%)	2 (1%)	8 (3%)	1 (1%)	11 (2%)
Restlessness	11 (2%)	1 (<1 %)	5 (2%)	2 (1%)	9 (1%)
Vascular disorders	62 (8%)	18 (7%)	28 (10%)	38 (20%)	84 (11%)
Hypotension	35 (5%)	9 (3%)	12 (4%)	19 (10%)	40 (5%)
Labile blood pressure	13 (2%)	3 (1%)	4 (1%)	14 (8%)	21 (3%)
Hemodynamic instability	10 (1%)	3 (1%)	7 (3%)	2 (1%)	9 (1%)
Nervous system disorders	25 (3%)	10 (4%)	7 (3%)	9 (5%)	26 (3%)
Renal and urinary disorders	20 (3%)	14 (5%)	3 (1%)	4 (2%)	21 (3%)
Musculoskeletal and connective tissue disorders	18 (2%)	4 (1%)	2 (1%)	2 (15)	8 (1%)

The key comparisons should be between all clevidipine and all comparators. In each of the positive control studies, subjects were randomized randomized in a 1: 1 ratio, and since the studies differed in the time when the effect on blood pressure control was initiated, the only meaningful comparison for safety is the comparison of clevidipine against all comparators. In comparing the clevidipine to the sun of active comparators, there are minimal differences between these treatments. That is not to imply that there were no adverse events associated with clevidipine but that in this complex population the signal of adverse events between active treatments cannot be discerned from the noise.

It should be noted that there hypotension and tachycardia were not always captured as adverse events because they were easily reversed by decreasing the dose of the infusion.

There is little experience with the use of beta-blockers to treat tachycardia and the most appropriate maneuver appears to temporarily decrease the dose until the tachycardia reverses.

Appendix

DMETS concerns (Verbatim)

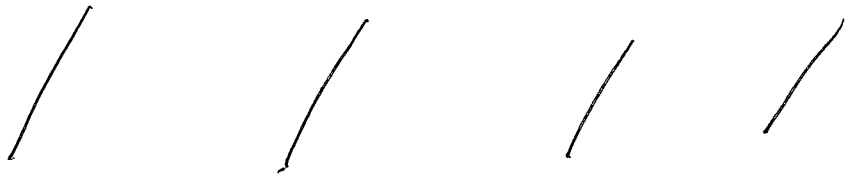
A. General Comments

1. DMETS recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Karl Stiller (the Project Manager assigned to the LNC), and the assigned ONDQA Chemist regarding the proper designation of the established name.

   DMETS recommends deleting ~ from the established name ~

2. The storage conditions for Cleviprex are unconventional and may be prone to error. First, the product should be protected from light until administration, thus, according to the How Supplied/Storage and Handling section of the package insert, it is described as "vials ~ ~ In reality, the vials may be removed from the carton in order to conserve space when storing the product. Secondly, since Cleviprex must be used within 2 months after it is removed from the refrigerator and placed at room temperature, the potential exists for practitioners to forget to date the carton or vial once it is removed from refrigeration, since this is not common practice for practitioners to label the product with an expiration date once it has been removed from refrigeration. In this case, there will be no way of knowing when the product should be used by and when it should be discarded. DMETS envisions that cartons and/or vials may be sent to the unit (i.e., ER, ICU, CCU) without any information identifying when the drug was placed at room temperature. Therefore, we anticipate the medication being discarded or returned to the pharmacy and perhaps returned back to the refrigerator (which is contraindicated).

   DMETS is not certain what the clinical consequences of these errors because the package insert ~



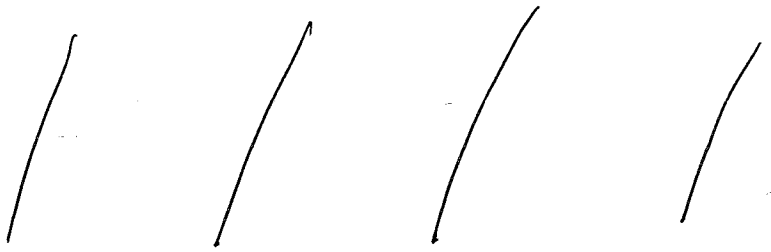
3. The dosage form should appear in conjunction with the established name. The complete established name should be at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2). For example:

   Cleviprex
   (Clevidipine Emulsion) for Injection

4. The strength is only expressed as total drug content (e.g., 25 mg/50 mL and 50 mg/100 mL). Since this vial is not a single dose product, it is important to have the mg/mL amount present on the label to convey the volume needed for a single dose. In addition to the total drug content, the product strength expressed in milligrams per milliliter should appear beneath the total drug content as noted below:

25 mg/50 mL (0.5 mg/mL)	50 mg/100 mL (0.5 mg/mL)

   Please revise accordingly.



B. Container Labels (50 mL and 100 mL vials)

1. See General Comments.

2. In order to increase the prominence of the information related to the safe administration of Cleviprex, we recommend the following revisions:

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

ONDAQA comments verbatim)

IV. List of Deficiencies Communicated to Applicant on 25-Feb-2008

Drug Substance:

- Deficiencies were sent to the DMF holder ( ) for the drug substance. Please ensure that the DMF holder responds to these deficiencies promptly.

- **S.4.1 Specifications**:
  a. List all known impurities separately in the drug substance release and stability specifications.
  b. Since [redacted] is a genotoxin and suspected carcinogen, the limit of [redacted] is not appropriate. The limit should be tightened to below the EMEA's Threshold of Toxicological Concern ([redacted] g/day).
  c. Please justify your proposed limit of [redacted] for [redacted] based on safety.
  d. Please include a test and acceptance limit for the specific rotation of the drug substance or provide justification based on data for why it is not needed.

Drug Product:

- Deficiencies were sent to DMF Holder [redacted] for the drug product. Please ensure that the DMF Holder responds to these deficiencies promptly.

- **P.5.1 Specification**: Please revise your specification to include a specific identity test for clevidipine butyrate, as your current test by HPLC retention time alone is not specific per ICH Q6A.

- **P.5.1 and P.5.6 Specification:** Please provide a scientific justification for your proposed limits of [redacted] each for [redacted] which give structural alerts for genotoxicity. As these limits would be [redacted] times (per genotoxin) the EMEA's Threshold of Toxicological Concern (TTC), a basic battery of genotoxicity tests should be conducted on these compounds separately and in combination to justify the proposed limits.

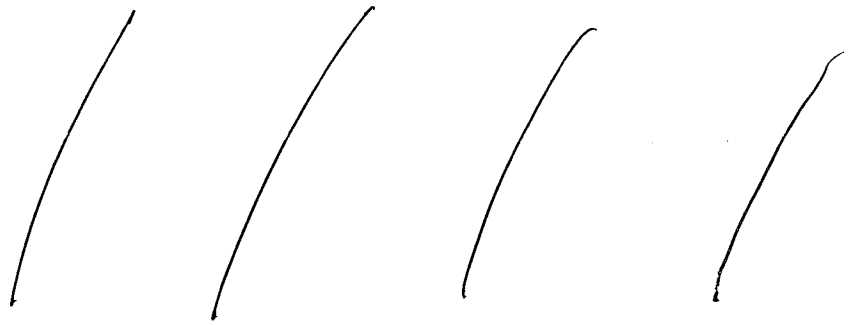
- **P.5.1 and P.5.6 Specification:** The limits for related substances [redacted] — both specified at NMT [redacted] were calculated based on the mean and a range factor of 4.5-fold of the standard deviation. Please use a factor of not more than three (3) for the calculation of range. Moreover, as these two impurities are [redacted] the limits should be tightened as much as possible.

- **P.5.1 and P.5.6 Specification:** The limit for Total Related Substances (proposed NMT [redacted] was calculated based on the mean and a range factor of 4.5-fold of

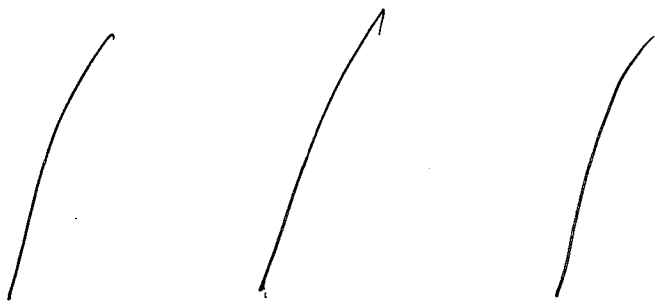
the standard deviation. Please use a factor of not more than three (3) for the calculation of range.

- **P.8.1 Stability:** Due to the differences between 100-mL and 50-mL bottles — e.g. the stability data for 100-mL bottles can not be extrapolated and applied to the 50-mL bottles. The stability data available to date for 50-mL fill size is 12-months, and this does not support a shelf-life. A shorter shelf-life (e.g. 24 months) must be used until supporting data for a longer shelf-life are provided.

- **P.8.2 Post-Approval Stability Protocol:** The proposed post-approval stability protocol is inadequate for the first three commercial batches. These studies should include long-term and accelerated (up to 6 months) conditions — the same as for the primary batches.

- 

- **Labeling and Packaging:**



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/s/

Abraham Karkowsky
5/13/2008 02:26:50 PM
MEDICAL OFFICER

COMBINED MEDICAL & STATISTICAL REVIEW

Application Type	NDA
Submission Number	22-156
Submission Code	SN 000
Letter Date	02-Jul-2007
Stamp Date	02-Jul-2007
PDUFA Goal Date	02-May-2008
Medical Reviewer Name	B. Nhi Beasley, Pharm.D.
Statistical Reviewer Name	John Lawrence, Ph.D.
Review Completion Date	07-March-2008
Established Name	clevidipine
(Proposed) Trade Name	Cleviprex ™
Therapeutic Class	calcium channel antagonist L-selective dihydropyridine
Applicant	The Medicines Company
Priority Designation	S
Formulation	intravenous emulsion, 0.5 mg/mL
Dosing Regimen	IV up to 72 hours
Indication	[redacted]
Intended Population	when oral antihypertensives are not feasible or desireable

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Abbreviations

α	alpha
AC	advisory committee
ACEI	Angiotensin Converting Enzyme inhibitor
AE	adverse event
AI	aortic insufficiency
alk phos	alkaline phosphatase
ALT	alanine aminotransferase
AM	asian male
AMI	acute myocardial infarction
ANCOVA	anaylsis of covariance
ANOVA	analysis of variance
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AV	aortic valve
BB	beta blocker
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CCB	calcium channel blocker
CEC	clinical events committee
CHF	congestive heart failure
CI	confidence interval
CI	contraindicated
CL	clearance
CLV	clevidipine
CM	cardiomyopathy
Cmax	maximum concentration
CMC	Chemistry Manufacturing Controls
CNS	central nervous system
COA	certificate of analysis
CRAC	CardioRenal Advisory Committee
CRF	case report forms
Css	concentration at steady state
CVA	cerebrovascular accident
CVD	cardiovascular disease
d	day
DB	double-blind
DBP	diastolic blood pressure
DCaRP	Division of Cardiovascular and Renal Products
DMF	drug master files
DR	dose response
DSI	Division of Scientific Investigations (FDA)
ECG	electrocardiogram
EMEA	European Medicines Agency
FDA	Food and Drug Administration

FDH	formaldehyde dehydrogenase
GC	gas chromatography
h	hour
HDL	high density lipoprotein cholesterol
HDPE	high density polyethylene
HM	hispanic male
HR	heart rate
HR	hazard ratio
hr	hour
HTN	hypertension
IABP	intra aoortic balloon pump
ICH	International conference on harmonization
IM	intramuscular
IND	investigational new drug
IV	intravenous
K	potassium
L	left
LBBB	left bundle branch block
LDL	low density lipoprotein cholesterol
LOCF	last observation carried forward
LOD	limit of detection
LOQ	limit of quantitation
MAP	mean arterial pressure
MC	multicentered
mg	milligram
MI	myocardial infarction
MIDCAB	minimally invasive direct coronary artery bypass
mL	milliliter
MV	mitral valve
NDA	new drug application
NIC	nicardipine
NMT	not more than
NR	not reported
NTG	nitroglycerin
OL	open label
OPCAB	off-pump coronary artery bypass
OSE	Office of Safety Evaluation
PBO	placebo
PC	placebo-controlled
PD	pharmacodynamic
PE	pulmonary embolism
PK	pharmacokinetic
PM	pharmacometric
ppm	parts per million
QD	once daily
QTc	QT interval corrected for heart rate
R	randomized
RT	room temperature

RV	right ventricle
RVAD	right ventricular assist device
s/p	status post
SAE	serious adverse event
SAP	stastical analysis plan
SAS	Statistical Analysis System
SB	single blind
SBP	systolic blood pressure
SDA	study drug administration
sens	sensitive
SL	sublingual
SNP	sodium nitroprusside
SOC	system organ class
sx	symptom
T1/2	half-life
tach	tachycardia
TEAE	treatment emergent adverse event
TG	triglycerides
TIA	transient ischemic device
Tmax	time to maximum concentration
tox	toxicity
tx	treatment
UK	United Kingdom
USP	united States Pharmacopeia
Vd	volume of distribution
VD	vasodilator
VTE	venous thromboembolic event
X	cross

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical and statistical perspective we recommend approval of clevidipine for the ~~~~~~~~~~~~~~~~~~~~ when oral treatments are not feasible or desirable. Clevidipine is an intravenous (IV) dihydropyridine calcium channel blocker (CCB) similar to the approved IV CCB nicardipine (with the exception of its metabolism – not by cytochrome P450 3A4 (CYP3A4)). Regarding efficacy, the results of two adequate, placebo-controlled studies, ESCAPE-1 and ESCAPE-2, for the primary endpoint of bailout to an alternative antihypertensive by 30 minutes, provide substantial evidence that clevidipine is effective in reducing blood pressure (BP) in the perioperative setting (pre, during, and post cardiac surgery). Regarding safety, clevidipine has an adverse event (AE) profile similar to that of other IV antihypertensives. It was studied directly against sodium nitroprusside (SNP), nicardipine (NIC) and nitroglycerin (NTG) in three large safety studies called ECLIPSE. The reviewer does not agree with the quick titration proposed by the sponsor, or the infusion duration of 72 hours since few subjects received clevidipine for 72 hours. Nonetheless, the reviewer feels that there is adequate information in the clinical program to assess efficacy and safety, and to write a set of dosing instructions for use.

1.2 Recommendation on Postmarketing Actions

There is no proposed risk management activity. The drug is to be infused for a short duration. There are no required Phase 4 commitments or other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clevidipine clinical program consists of 19 studies, with 99 healthy subjects and 1301 hypertensives patients who received at least one dose of clevidipine (1400 total clevidipine exposures). Fifteen studies evaluated clevidipine in hypertensives patients. There were 1093 perioperative hypertension, 82 essential hypertension, and 126 severe hypertension patients treated with clevidipine.

There were six Phase III studies, all conducted in the US. ESCAPE-1 and ESCAPE-2 were randomized, placebo-controlled studies, with roughly 100 patients in each study, which assessed the efficacy of clevidipine pre and post operatively, respectively. The largest safety data come from the three ECLIPSE trials that compare clevidipine to an active comparator (NTG, SNP, or NIC) in perioperative (pre, during and post cardiac surgery) hypertension. The ECLIPSE trials included a total of 752 clevidipine treated subjects. The VELOCITY study was a non-controlled, open-label study in severe HTN with 126 patients treated with clevidipine.

The mean duration of drug infusion was less than 24 hours in the six Phase III trials. Subjects in the ESCAPE studies received drug for 30 minutes on average, with the longest duration being 1 hour. The mean duration of infusion in the ECLIPSE studies was 8 hours (90% CI, 7.6 to 9.0 hours). The mean duration of infusion in VELOCITY was 21 hours (90% CI, 20 to 22 hours).

The initial starting dose in all Phase III studies was 0.4 ug/kg/min. VELOCITY specified the dose in mg/hr, with the initial dose being 2 mg/hr, roughly 0.4 ug/kg/min. The average infusion rate in ESCAPE was 1.88 ug/kg/min (90% CI, 1.6 to 2.1 ug/kg/min) or 9.8 mg/h. The average infusion rate in the ECLIPSE studies was 0.9 ug/kg/min (90% CI, 0.8 to 0.9 ug/kg/min) or 4.5 mg/h. In VELOCITY, the average infusion rate was 1.95 ug/kg/min (90% CI, 1.7 to 2.2 ug/kg/min) or 9.5 mg/hr. Thus, the average infusion rate was relatively low, considering the initial dose was 0.4 ug/kg/min and could go up to 8 ug/kg/min.

1.3.2 Efficacy

The sponsor studied two distinctly different patient populations in its Phase III studies; the perioperative cardiac surgery patient (ESCAPE), and the severe hypertension patient (VELOCITY). Both had target SBP reductions of 15% from baseline, although the absolute BP goals were different.

In the pivotal efficacy studies (ESCAPE-1 and -2), there were less bailouts in the clevidipine group compared to the placebo group (primary endpoint), 7.9% vs. 81.2%, respectively. Bailout was defined as the premature discontinuation of study drug infusion, for reasons of efficacy or safety, by 30 minutes after the start of the infusion. In ESCAPE, the time to 15% SBP lowering (secondary endpoint) was ~ 5-6 minutes using a dosing scheme of 0.4 ug/kg/min increased every 90 seconds until 3.2 ug/kg/min; thereafter the dose was increased by 1.5 ug/kg/min up to a maximum of 8.0 ug/kg/min. The time to an effect of 15% reduction in SBP (placebo and baseline subtracted) was 9 minutes in ESCAPE-1 (preoperative) and 7 minutes in ESCAPE-2 (postoperative). The maximal mean effect was -20/-22% (SBP/DBP) in ESCAPE-1 and -17/-16% (SBP/DBP) in ESCAPE-2.

The VELOCITY study showed 89% of subjects reaching target SBP range within 30 minutes of the infusion (co-primary endpoint). The amount of BP reduction was not prespecified, but was to be between 20-40 mmHg and the "usual and customary ~ 15%". In VELOCITY, where the dose titration occurred more gradually, the time to 15% SBP lowering was about 10 minutes (secondary efficacy endpoint) using a dosing scheme of 2 mg/hr doubled every 3 minutes to a maximum dose of 32 mg/h. If patients did not reach target SBP within 30 minutes, an alternate IV antihypertensive was allowed +/- clevidipine.

Unfortunately, all studies contained concomitant IV antihypertensive use during study drug administration (SDA). Concomitant use was low in ESCAPE-1, with only 2 out of 53 treated clevidipine patients taking a vasodilator during the first 30 minutes of SDA. Use was much higher in ESCAPE-2 (25 out of 61 clevidipine treated patients) predominantly due to the use of NTG. In VELOCITY 8.7% of patients (n=11) used an IV antihypertensive with clevidipine, and 6.3% (n=8) used an IV antihypertensive without clevidipine.

It is unclear how a titration interval of every 90 seconds or every 3 minutes was chosen. The reviewer found that after reviewing the fixed dose studies, the maximal effect is observed around 10-15 minutes after the infusion is started.

As mentioned earlier, the mean infusion duration in the Phase III studies was less than 24 hours.

Clevidipine was titrated to effect in these Phase III studies. The dose could be titrated, stopped, reduced, and restarted at the investigators' discretion. The reason for dose changes were not noted in the case report forms (CRFs). The non-specific dose alterations, use of concomitant IV antihypertensives, and sedatives make the assessment of dose response difficult.

These Phase III efficacy studies demonstrate that clevidipine lowers BP and can be used in the perioperative and postoperative setting as well as in severe hypertensives (although the severe HTN study was uncontrolled and open-label). Clevidipine does not seem to offer any advantage over other approved IV antihypertensives.

1.3.3 Safety

The safety database includes 1400 subjects that received at least one dose of clevidipine. The largest safety data come from the three ECLIPSE trials that compare clevidipine to an active comparator in perioperative (pre and during cardiac surgery for ECLIPSE-NTG and ECLIPSE-SNP and post cardiac surgery for ECLIPSE-NIC) hypertension. The primary endpoint was the incidences of death, stroke, MI and renal dysfunction in the clevidipine and active comparator groups from the initiation of study drug infusion through postoperative Day 30. A blinded Clinical Events Committee (CEC) adjudicated the occurrence of the primary endpoint events. However, there was no prespecified alpha apriori for these endpoints combined or individually. Sample size in all three trials was arbitrarily chosen. An independent DSMB reviewed safety data in an open-label manner. The mean study drug duration in ECLIPSE was 8 hours. Given that the elimination half-life is 1 hour, most of the drug is gone by 5 hours after the dose. Thus, relating causality to safety assessments made out to 30 days does not make much sense. Deaths in the clevidipine program occurred mostly in cardiac surgery patients. There was only one death that could have been attributable to clevidipine. There was no difference in death, stroke, MI or renal dysfunction at 30 days between clevidipine and active comparators (SNP, NIC, and NTG). While serious adverse events (SAEs) were assessed out to 30 days, adverse events (AEs) were assessed out to 7 days.

There were no SAEs in essential HTN or healthy volunteers that received clevidipine. The most common SAE in the perioperative patient was cardiac disorders, with afib being the most common cardiac disorder. The rate was no different than that in active comparators. Cardiac disorders was the most common SAE across the five perioperative studies, except for ECLIPSE-NIC (respiratory, thoracic and mediastinal disorders was more common). Nervous system disorders were more common in severe HTN, however only 12 patients total had SAEs.

The most common reason for an AE leading to discontinuation was headache in healthy subjects, and hypotension and hypertension in hypertensive subjects.

The most common AE in essential HTN was headache, polyuria, infusion site reaction, and nausea. The most common AE for clevidipine in perioperative patients were incision site complications, atelectasis, and atrial fibrillation. Headache was the most common AE in the severe HTN group. Headache was also the only AE that seemed to be related to dose. Hypotension was most likely an under reported AE. Since the drug's effect is to reduce BP, investigators were told not to report hypotension as an AE if it could be controlled by reducing or stopping the dose or by other means.

Clevidipine causes a reflex tachycardia of about 5-12%. There was not extensive experience with its use with beta blockers. Rebound HTN seemed to be dose related, with a placebo adjusted mean change from baseline SBP of 9% for the 16 mg/h dose group.

Atrial fibrillation was the most common cardiac disorder in perioperative patients (30%). The ECLIPSE studies were temporarily stopped due to a greater incidence of afib in clevidipine treated patients compared to active control (AC). The sponsor conducted an extensive retrospective review of the data which resulted in similar incidence rates of afib between the 4 treatments (CLV, SNP, NTG, and NIC).

Overall, the AE profile was similar to active comparators. There is reflex tachycardia and rebound HTN.

1.3.4 Dosing Regimen and Administration

The dosing regimen used in the clinical program for perioperative HTN was 0.4 ug/kg/min doubled every 90 seconds until 3.2 ug/kg/min; thereafter the dose was increased by 1.5 ug/kg/min up to a maximum of 8.0 ug/kg/min. Rates between 4.4 – 8.0 ug/kg/min were only allowed for 2 hours during a 24 hour period. Due to lipid load restrictions, no more than 500 mL of clevidipine infusion (formulated in 20% lipid) was to be administered in the first 24 hour period, and the maximum amount of lipid that may be administered was 2.5 g/kg/24h.

The dosing regimen used for severe HTN was 2 mg/hr doubled every 3 minutes until a maximum rate of 32 mg/h was reached.

The sponsor is seeking dosing instructions based on mg/hr, which the reviewer believes is acceptable based on pharmacokinetic information. The initial starting dose of 2 mg/hr also seems reasonable based on dose finding studies. The reviewer does not agree with the quick titration of every 90 seconds [redacted], and thinks this should be every 10-15 minutes since the maximal effect in fixed dose studies is observed around 10-15 minutes after the start of the infusion. Waiting 10-15 minutes would avoid the potential to cause hypotension. The reviewer also disagrees with the proposed duration of 72 hours, since the duration of use in the ESCAPE trials was on average 30 minutes, in ECLIPSE 8 hours and in VELOCITY 21 hours. Study 06-01 did give clevidipine as a continuous infusion for 72 hours, however only 47 subjects received drug for this long. Thus, the reviewer recommends a duration of use of 24 hours.

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted due to the short-term use of clevidipine. Clevidipine and its major metabolite, M1, were found to be inducers of CYP3A4. Clevidipine also has some inhibitory effects on CYP2C9, 2C19, 2D6, and 3A4.

1.3.6 Special Populations

There were no differences in effect by gender, race, or age. However, the patient population studied was mostly Whites, except for the severe HTN study which included mostly Blacks. There were no formal studies that assessed the effect of hepatic or renal insufficiency on clevidipine.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

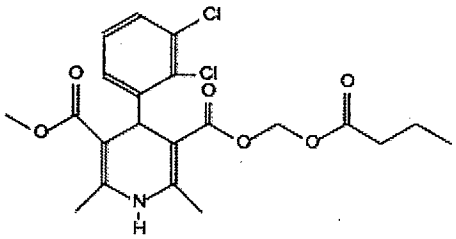
Clevidipine butyrate is an intravenous dihydropyridine calcium channel blocker. Clevidipine drug substance is a racemic mixture of two equally active enantiomers, (+)-S and (-)-R. The chirality is caused by the asymmetrically substituted benzylic carbon. Its complete chemical name is

Butyroxymethyl methyl 4-(2',3'-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate

4-(2',3'-Dichlorophenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid, 3-butyryloxymethyl ester 5-methyl ester.

It has a molecular weight of 456.3 mg/mL, a molecular formula of $C_{21}H_{23}Cl_2NO_6$ and the structure is shown in the following figure. It is also referred to as H324/38.

Figure 1. Clevidipine butyrate structure



Clevidipine is a [redacted] that is practically insoluble in water, [redacted]. Clevidipine is formulated in Intralipid®. Clevidipine emulsion contains the same excipients at the same concentrations as the marketed formulation of 20% Intralipid including soybean oil [redacted], glycerin [redacted], egg yolk phospholipids [redacted], sodium hydroxide as the pH-adjusting agent [redacted]

Clevidipine emulsion in bottles is a preservative-free sterile product presented for single use as an IV infusion without dilution. It is available in 50 mL or 100mL glass vials at the strength of 0.5 mg/mL.

In the six Phase III studies, clevidipine was supplied as a sterile, white, opaque liquid in 100 mL (all studies except VELOCITY) single use glass bottles at a concentration of 0.5 mg/mL in a 20% lipid emulsion. ECLIPSE-SNP, -NIC, and VELOCITY studies had 50 mL bottle supplies. Once the seal was punctured, the study drug had to be used within 12 hours.

Clevidipine butyrate intravenous emulsion should be stored refrigerated at 2-8°C (36-46°F). The sponsor states that vials in cartons may be transferred to 25°C (77°F, USP controlled room

temperature (RT)) for up to 2 months. It should not be returned to the refrigerator after being stored at RT. It should be protected from light until administration. The Sponsor states that it does not need light protection during administration. This aspect needs to be finalized in the Chemistry review.

Admixture compatibility at a ratio of 1:1 has been established with water for injection, normal saline, 5% dextrose, lactated ringers solution, 10% amino acid, 5% dextrose in normal saline, and 5% dextrose in ringers lactate. No incompatibilities have been observed with glass vials or ethylene vinyl acetate bags and administration sets. Clevidipine emulsion

2.2 Currently Available Treatment for Indications

There are eight intravenous drugs approved for the treatment of hypertension. One is also a dihydropyridine. See table.

Table 1. Properties of available intravenous medications for HTN

	class	onset	offset	duration	T 1/2
sodium nitroprusside	n/a	Rapid 1-2 min	rapid	1-10 min	Rapid 2 min
nicardipine	CCB	slow	30-40 min	NR	14 h
nitroglycerin	nitrate	2 min	rapid	10-20 min	3 min
labetolol	α + BB	5 min	NR	16-18 h	5.5 h
enalaprilat	ACEI prodrug	15 min	NR	6 h	11 h
esmolol	BB (1-selective)	< 5 min	10-20 min	10-20 min	9 min
fenoldopam	D_1 agonist	5 min	5 min	30-60 min	5 min
hydralazine	n/a	10-80 min	NR	6-8 h	54 min

Adapted from pg. 10 of Sponsor's Clinical Overview
T ½=elimination half life, min=minute, h=hour
NR=not reported
α=alpha, ACEI=angiotensin converting enzyme inhibitor, BB=beta blocker, CCB=calcium channel blocker, D_1=dopamine

The table that follows provides some insight into the complexity of the dosing recommendations for the approved IV antihypertensives. Half are dosed by weight. Five must be given by constant infusion.

Table 2. Doing instructions for available intravenous medications for HTN

	Dosing instructions
Sodium nitroprusside (SNP)	0.3 ug/kg/min titrate up every few minutes until desired effect or max of 10 ug/kg/min. Give 10 ug/kg/min for no more than 10 minutes. Average dose 3 ug/kg/min. Titration increment not stated.
nicardipine	50 mL/hr (5.0 mg/hr), increase by 25 mL/hr (2.5 mg/hr) every 15 minutes up to a maximum of 150 mL/hr (15 mg/hr) until desired BP achieved
nitroglycerin	5 ug/min, increase by 5 ug/min every 3-5 min. If no response at 20 ug/min, increments of 10 ug/min and later 20 ug/min can be used.
labetolol	Two sets of dosing instructions (repeat IV injection or continuous infusion) • 20 mg (0.25 mg/kg) IV over 2 min, then 40 or 80 mg every 10 minutes, until a TOTAL of 300 mg. • 2 mg/min, titration increment not given, but stated that effective dose is 50 – 200 mg. A total dose of 300 mg may be required in some patients.
enalaprilat	1.25 mg over 5 minutes every 6 hr IV
esmolol	Two sets of instructions for intra and postoperative tachycardia and/or HTN * Loading dose 1 mg/kg bolus over 30 seconds f/b 150 ug/kg/min, adjusted up to 300 ug/kg/min maintenance infusion * Loading dose 500 ug/kg/min over 1 minute f/b 50 ug/kg/min, adjusted every 4-5 min up to 300 ug/kg/min
fenoldopam	0.01 – 0.3 ug/kg/min, titrate every 15 minutes by 0.05 – 0.1 ug/kg/min, up to 1.6 ug/kg/min
hydralazine	20-40 mg injection (IM or rapid IV bolus), repeat as necessary

SVT=supraventricular tachycardia, f/b=followed by

The following table lists the approved indication for the intravenous antihypertensives.

Table 3. Indication and notes for available intravenous medications for HTN

	Indication	Notes
sodium nitroprusside	*reduce BP in hypertensive crisis *controlled hypotension to reduce bleeding during surgery *acute CHF	Light sens; dosing guidelines for children; Methemoglobinemia & thiocyanate toxicity; caution in hepatic and renal (cyanide tox); Reconstitute twice
nicardipine	Short-term tx of HTN when oral therapy is not feasible or not desirable	Light sens; Caution CHF, impaired renal or hepatic function
nitroglycerin	*Tx perioperative HTN *Control CHF during AMI *Tx angina when unresponsive to SL NTG and BB *Induction of intraoperative hypotension	Tolerance Reflex tach CI in conditions dependent on venous return (tamponade, restrictive CM, constrictive pericarditis) Light sensitive
labetolol	Control of BP in severe HTN	Neg inotropic and chronotropic effects *caution in hepatic impairment *postural hypotension
enalaprilat	Treatment of HTN when oral therapy is not practical	angioedema
esmolol	*Rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short acting agent is desirable. *noncompensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. *treatment of tachycardia and HTN that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated.	Neg inotropic and chronotropic effects *caution in renal impairment
fenoldopam	*in-hospital, short-term (48 hours) management of severe HTN when rapid, but quickly reversible, emergency reduction of blood pressure is indicated, including malignant HTN with deteriorating end organ function.	Weight based dosing Causes tachycardia *also has pediatric indication *caution with beta-blocker due to inhibition of the sympathetic reflex response to fenoldopam
hydralazine	Severe essential HTN when the drug cannot be given orally or when there is an urgent need to lower BP	IV bolus & IM; lower dose in renal impairment

tx = treatment; SL NTG = sublingual nitroglycerin

2.3 Availability of Proposed Active Ingredient in the United States

Not marketed in the USA.

2.4 Important Issues With Pharmacologically Related Products

Nicardipine and fenoldopam were the subject of a Cardio-Renal Advisory Committee meeting. The major issues for each drug are discussed below.

Nicardipine injection, NDA 19-734, was discussed at the June 15, 1990 CRAC meeting. Oral nicardipine was already approved for the treatment of hypertension and angina pectoris. Intravenous nicardipine was evaluated in 348 hypertensives: 165 severe, 153 postoperative, and 30 mild to moderate. Treatment for hypertension was evaluated in two placebo-controlled studies, one in postoperative hypertensive patients and the other in severe hypertensive patients (n=247, of which 243 received IV nicardipine). Placebo patients that failed therapy were put on open-label nicardipine. The PK were reasonably described in a 48 hour infusion study in mild to moderate hypertension for the lower dose of 4 mg/hr, but not for higher doses. The exact duration of action had not been determined. Individual response (onset and amount of reduction) was variable. Major side effects included headache, nausea and vomiting, tachycardia, and atrial fibrillation. Hypotension lasted for several hours. The committee voted (5 yes, 2 no) to label all marketed IV agents for the second line treatment of hypertension, for the removal of severe hypertension. The committee voted (6 yes, 1 no) to approve IV nicardipine for the treatment of hypertension when oral therapy is neither feasible nor desirable.

Intravenous fenoldopam, a D1 receptor agonist, was discussed at the June 26, 1997 CRAC meeting. The development of the oral formulation was stopped due to poor bioavailability and short half-life. The sponsor conducted 10 trials in severe HTN with the intravenous formulation. The 10 trials showed mean reductions from baseline in DBP ranging from 24 to 33 mmHg with doses of 0.1 – 0.3 ug/kg/min. Two trials included SNP as a comparator and found both drugs reduced BP comparatively. A comparison in post-op HTN was made with nifedipine whereby target BP was achieved more quickly with fenoldopam. Based on these trials, Smith Kline filed an NDA for fenoldopam, but was issued a no approvable letter citing two deficiencies. First the relationship between PK and PD had not been explored in hypertensive patients, hence appropriate directions for use could not be written because the dosing regimen had not been defined. Second, the patient population studied was severe hypertension and thus did not support the approval for the treatment of malignant HTN. Constant rate IV infusion was not defined, the study designs were primarily titration to effect in nature and there was little information on onset or offset of drug effect during prolonged infusions. Rebound and tolerance had not been adequately addressed. The sponsor (now Neurex) then conducted two trials (PK/PD multiple fixed doses for 48 hours in HTN and multiple fixed doses in hypertensive emergencies) plus a renal function study. These studies demonstrated that the dose response curve was similar between hypertensive populations. The effect was predictable, thus instructions for use could be written, and there was no evidence of acute, ongoing end organ damage. The entire clinical program included 1,009 patients and 259 healthy subjects treated with IV fenoldopam.

Headache, nausea, and hypotension were the most frequent AEs with AE event similar to SNP in a 200 patient trial. There were a total of 19 deaths; only two were in the hypertension studies, occurred off therapy and were unrelated to drug. The AC wanted more information on the use of fenoldopam with a beta blocker. The AC voted (9 yes, 1 no) to approve the drug for people who cannot take oral medication. The AC voted (8 yes, 2 no) to approve the drug for a specific indication such as severe hypertension, malignant hypertension or hypertensive crisis (as opposed to the nonspecific indication of "for people who cannot take it orally").

2.5 Presubmission Regulatory Activity

There were six general meetings between DCaRP and the sponsor (March and August 2003, July and December 2004, March 2006 and January 2007). Since similar topics were discussed, this section is organized by topic and not by date.

Population/indication – Most of the development program was conducted in patients undergoing cardiac surgery (mainly CABG). The Division told the sponsor that the efficacy studies were suitable for the proposed indication of [redacted] but not [redacted] when oral therapy is not feasible or not desirable" because of the insufficient number of non-surgical patients. The Division accepted the proposal of including 100 patients with severe hypertension. The Division told the sponsor that the label will reflect the data. At the PreNDA meeting, [redacted]

Study design and endpoints – The Division accepted the study designs (efficacy studies blinded and safety studies open-label) and primary endpoint of bailout in the two pivotal efficacy trials. The safety studies should contain blinded central adjudication of the serious AEs.

Clinical pharmacology – The Division advised the sponsor to determine the enantiomer's efficacy and safety.

Because there were no significant drug interactions in-vitro, the Division agreed that no clinical drug-interaction studies were required (2004). However, at the PreNDA meeting, it was discovered that clevidipine inhibits a number of isoenzymes and the Division wanted to know the fate and pharmacologic activity of the metabolite, M1. It was decided that because of the short infusion duration, no additional studies (including renal impairment) were required; however [redacted]

Formaldehyde – The Division told the sponsor to determine if formaldehyde accumulates with treatment, stating that levels should be measured in patients. The sponsor stated that it is only in-vivo that clevidipine converts to formaldehyde, however the sponsor proposed to measure formic acid, stating that formaldehyde assays have not been validated and formaldehyde quickly converts to formic acid. The Division told the sponsor to substantiate that formic acid concentrations were better than formaldehyde concentrations. The sponsor proposed a human study in July 2004, but it was agreed that the study would not determine where the conversion of

clevidipine to formaldehyde takes place, and if the formation of formaldehyde is distributed and centralized in a specific organ. Thus, an animal study with radiolabeled clevidipine was conducted to determine where clevidipine is converted to formaldehyde.

The sponsor would also provide observational data to address the Division's concerns about the potential safety issue with the formation of formaldehyde.

The reverse bacterial mutation assay was repeated using formaldehyde dehydrogenase (FDH) on the premise that this would decrease the number of revertants generated. However, the study did not show a decrease in revertants in the presence of FDH. Thus, not supporting the original premise. The sponsor then conducted a third study containing FDH controls confirming that formaldehyde was responsible for previous results in-vitro. The Division agreed that the data would now be sufficient to address their concerns.

QT prolongation – For the assessment of QT prolongation, it was agreed that the sponsor would study the maximum tolerated dose over steady state of the metabolite, maintaining the dose for 15 minutes. The study design was discussed in December 2004 and April 2006. The Sponsor concluded that their was no QT effect, however the Division stated that there were marked increases in heart rate and the data needed further evaluation.

PK/PD – The Division suggested the sponsor model the PK- BP effect and demonstrate that there is no hysteresis of the concentration dynamic effect upon discontinuation of a long infusion. The sponsor should also demonstrate clevidipine's safety with infusion times longer than 18 hours. The Sponsor should provide PK data after 72 hours of exposure in their PK/PD study. The results should provide reassurance of the kinetics with longer infusions since the current data seem to indicate a change in clevidipine PK with higher doses and increased infusion times. The Division stated

Dosing – Based on PK results, a non-weight based approach might be justified.

CMC – The Sponsor is to continue excipient testing for product release.

Other – Determine if intralipid has an acute effect on BP (in case the sponsor wants to use a different vehicle in the future). The Sponsor reassured DCaRP of the safety of beta blockers for controlling clevidipine provoked tachycardia.

2.6 Other Relevant Background Information

The product is not marketed in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

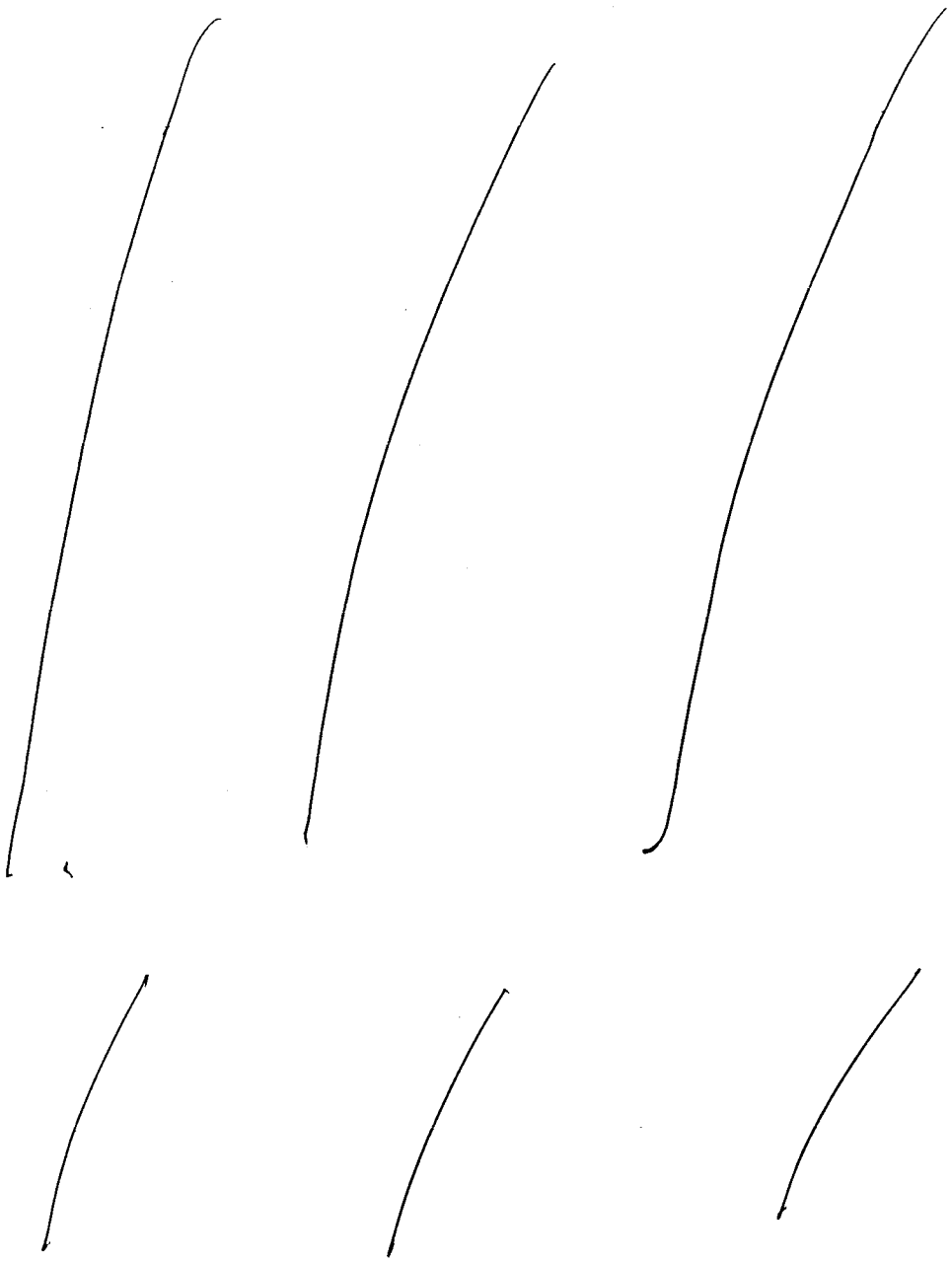
For a complete review, see the Chemistry and Microbiology reviews. This summary is based on the Chemistry Initial Quality Assessment dated 27-Jul-2007 by Dr. Kasturi Srinivasachar, the final Chemistry Drug Master Files (DMF) — drug substance review by Dr. Monica Cooper dated 17-Dec-2007 and DMF — deficiency letter sent to the sponsor dated 17-Jan-2008.

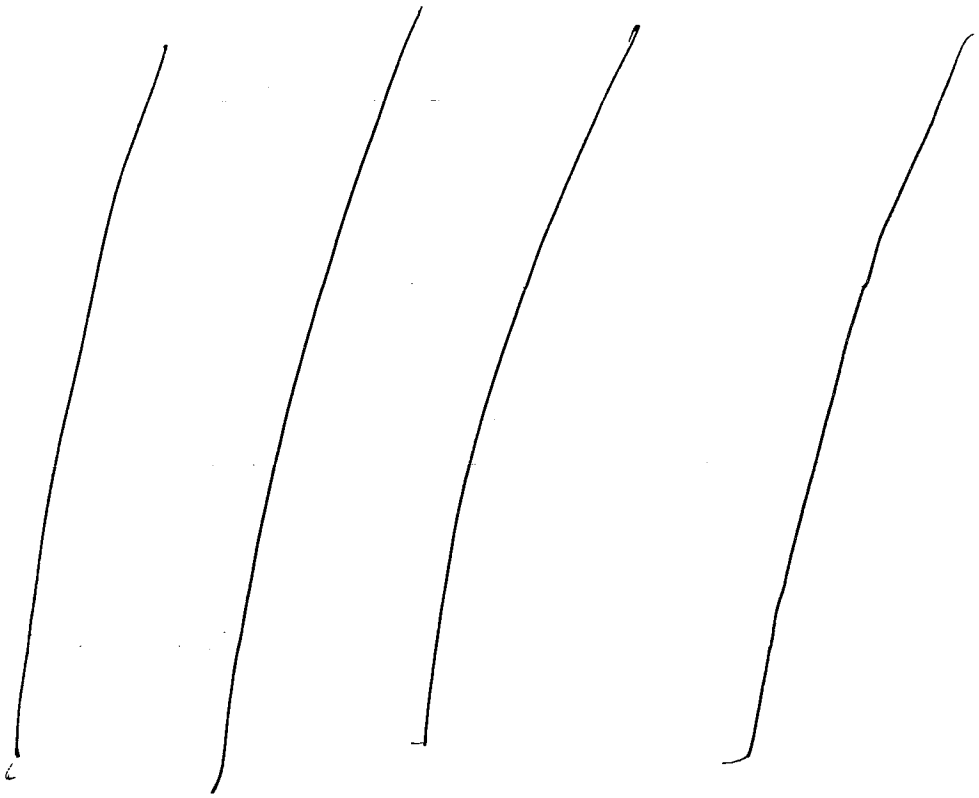
The Microbiology review (Dr. Bob Mello) and final Chemistry reviews by Drs. T. Chang and Monica Cooper were not available. The Chemistry reviews will also include DMF — - preliminary discussions are that it is adequate), DMF — (drug product – preliminary discussions are that it is inadequate), and the NDA review (preliminary discussions are that there are many deficiencies).

The Microbiology review will be important because this is a parenteral dosage form; thus sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life is a potential issue. This is — Clevidipine is prone to — degradation and the Sponsor has proposed storage at 5±3° C for the drug product. — Because of this, the studies demonstrating compatibility of the product with — need careful evaluation.

The parts of DMF — that were adequate are summarized. The holder adequately described the general properties of the drug substance, characterized the drug substance, and described the manufacturing process. — potential impurities were identified and the relative response factors, LODs (limit of detection) and LOQs (limit of quantitation)for each impurity were determined. The applicant provided a detailed description of each of the analytical procedures. Batch data for 5 batches was presented. The designated container closure system was appropriate for bulk storage of the drug substance.

Despite all of the above, the DMF was inadequate for support of this NDA. Fourteen deficiencies were sent on 17-Jan-2008 to the DMF holder, [redacted] They include the following:





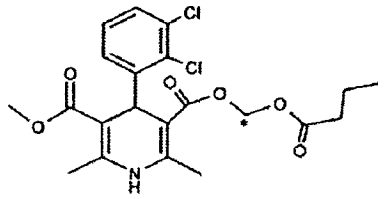
3.2 Animal Pharmacology/Toxicology

This summary is based on the Pharm/Tox draft review dated 28 January 2008 by Dr. Elizabeth Hausner. Please see the final review for complete pharmacology/toxicology information. Dr. Hausner has three major recommendations. She recommends it be approvable with resolution of the genotoxicity issue. She recommends an in-vitro receptor binding study, and her third recommendation can be found in the Labeling review section 10.2.

The potential genotoxicity is the most critical aspect of the pharmacology/toxicology review. Formaldehyde, a known genotoxicant, is a metabolite of clevidipine. The ratio for formaldehyde metabolite generation was not determined, but based on the structure similarity to the main metabolite a ratio of 1:1 is expected. The main metabolite H152/81 is produced in a 1:1 ratio with the parent drug (by ester hydrolysis). The sponsor has only provided the theoretical calculations of the amount of formaldehyde produced and the effect on endogenous levels. There were a plethora of positive genotoxic assays in this NDA. Formaldehyde was used as a positive control in some of the assays and formaldehyde dehydrogenase (FDH) was used to determine if the positive results were attributable to the formaldehyde. In some cases, clevidipine produced greater positive responses than formaldehyde alone. The use of FDH did not completely resolve the positive assay results. Therefore, either there are other genotoxins in the drug substance or clevidipine itself has genotoxic potential.

Formaldehyde is widely distributed. Study PK04-095, report QKAN-2005-0692-ADM, examined the tissue distribution of ^{14}C-clevidipine in male Sprague-Dawley and Long Evans rats following a single IV bolus dose. The ^{14}C label was in the formaldehyde portion of the side chain so that ^{14}C-formaldehyde would be produced from the metabolism of clevidipine (see figure). There was widespread distribution of radioactivity with maximum observed concentrations in tissues around 0.5 – 8 hours post-dose.

Figure 2. Position of ^{14}C radiolabel, PK04-095



Clevidipine

* designates ^{14}C radiolabel position

The highest values of radioactivity were seen in the pancreas, thyroid, and bone marrow of albino rats. High levels were also seen in the bone marrow and thyroid of pigmented rats. Radioactivity was measurable in the testes, accessory sex organs, eyes, and CNS for at least 672 hours after dosing. Drug associated radioactivity was associated with the melanin-containing tissues in the eye and skin. Drug derived radioactivity was higher in pigmented vs. non-pigmented skin.

General toxicology assessments were confounded by the intralipid vehicle which caused clinical chemistry and histologic effects consistent with its lipid dense nature.

No carcinogenicity studies were performed because of clevidipine's proposed short-term use. The America Conference of Governmental Industrial Hygienists lists formaldehyde as a suspected human carcinogen (A2) and the Environmental Protection Agency calls it a probable human carcinogen (B1).

The reproductive toxicology effects are typical of those seen with other CCB: dystocia, delayed parturition, and impaired male fertility. Atypical of CCBs was that there was unusual or atypical estrous cycle length and pseudopregnancy.

The safety pharmacology was incomplete. Neither pulmonary nor overt behavioral effects have been studied. The assessment of cardiovascular effects was done in an atypical manner, but showed no discernable QTc lengthening or other adverse effects in anesthetized dogs. Clevidipine did not influence spontaneous HR or AV conduction in vitro and did not cause negative chronotropic or dromotropic effects in vivo. Reflex tachycardia was observed in non-anesthetized animals.

A dose related inhibition of gastric emptying and propulsive intestinal movements was seen, consistent with other calcium channel blockers and the propensity to cause constipation.

Clevidipine-associated radioactivity was rapidly and widely distributed (Report PK04-095) and persisted. The radio-labeled portion of the molecule ($^{14}CH_20$) persisted in the various tissue sampled until the last point of determination (28 days). The sponsor's statement that radioactivity is completely eliminated within 8 days is inconsistent with the data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data for this review include the sponsor's NDA submission, package inserts from antihypertensives listed in Section 2.2., fenoldopam advisory committee minutes dated June 1997, nicardipine advisory committee minutes dated June 1990, nicardipine memo from the executive secretary of the CRAC to the CDER Director dated 20 June 1990, the DSI consults dated 09 Nov 2007 and 25 Jan 2008, the DMETs consult dated 20 Dec 2007, the pharmacometric draft review dated 28 January 2008, the QT IRT team final review dated 03 Dec 2007, the final Chemistry drug substance DMF — review dated 12 Dec 2007, the Chemistry Initial Quality Assessment dated 27 Jul 2007, and the Pharm/tox draft review dated 28 Jan 2008. No other draft reviews were available at the time this was finalized.

Clevidipine was developed throughout the end of Phase II by AstraZeneca. All AstraZeneca studies are prefixed by SAD (shot-acting dihydropyridine)-XXXX. All studies conducted by the sponsor are prefixed by TMC-CLV-XX-XX (The Medicines Company).

4.2 Tables of Clinical Studies

The clinical development program includes 19 studies of which six were Phase III studies. Of these, two were placebo-controlled efficacy studies in perioperative hypertensive patients, three were active-controlled, safety studies in perioperative hypertensive patients, and one was a non-controlled study in severe hypertensive patients. These six were included in the sponsor's ISE (grayed in table that follows). All were included in sponsor's ISS. The following table lists all studies by hypertension/subject type in chronological order.

Table 4. Table of clinical studies

			N treated (clev/other) Safety Eval	Primary Objective	Population	Control	Dose per protocol*	Follow-up (days)	Study Dates Sites
Trials included in ISE (6 Phase III)			**1846 (992/854)**						
Perioperative HTN			**1720**						
TMV-CLV	03-01	ESCAPE-1	104 (53 / 51)	Pre-op BP effect assessed by bailout in 30 min	Cardiac surg CABG, OPCAB, MIDCAB, Valve	Pbo DB parallel	0.4 ug/kg/min, doubled every 90 seconds up to 3.2 ug/kg/min. Doses greater than 3.2 were increased by 1.5 ug/kg/min, to a maximum of 8 ug/kg/min. 30 min or bailout, max 1 h	Day 7 or discharge	1/2004 – 11/2004 USA (12)
TMV-CLV	03-02	ESCAPE-2	110 (61 / 49)	Postop BP effect assessed by bailout in 30 min	Cardiac surg Same as above	Pbo DB parallel	Same as above	Day 7 or discharge	12/2003-10/2004 USA (15)
TMC-CLV	03-03	ECLIPSE-NTG	546 (268 / 278)	Safety (Death, stroke, MI, renal dysfunction, no prespecified alpha apriori)	Cardiac surg Same as above PI determined periop HTN. HTN not defined	NTG	0.4 ug/kg/min, doubled every 90 seconds up to 3.2 ug/kg/min. Doses greater than 3.2 were increased by 1.5 ug/kg/min, to a maximum of 8 ug/kg/min Dosed until discharge from ICU 4.4 – 8.0 ug/kg/min allowed for only 2 h in 24 h	Post-op Day 30 phone	4/2004 – 10/2005 USA (28)

			N treated (clev/other) Safety Eval	Primary Objective	Population	Control	Dose per protocol*	Follow-up (days)	Study Dates Sites
							Max of 2.5 g/kg/24 h (lipid load restriction)		
TMC-CLV	03-04	ECLIPSE-SNP	579 (296 / 283)	Safety	Cardiac surg PI determined periop HTN	SNP	Same as above	Post-op Day 30	6/2004 – 10/2006 USA (35)
TMC-CLV	03-05	ECLIPSE-NIC	381 (188 / 193)	Safety	Cardiac surg PI determined post op HTN	NIC	Same as above	Post-op Day 30	5/2004 – 9/2006 USA (28)
Severe HTN			**126**						
TMC-CLV	06-02	VELOCITY	126	%SBP below lower level target in 3 min (safety) % pts reach target SBP in 30 min (efficacy) Titration to SBP target (-20 to -40 mmHg, ~15% anticipated reduction	Severe HTN	Non-control Alt antiHTN allowed +/- CLV	2 mg/h, doubled every 3min, 32 mg/h max	7 days after infusion start (phone call)	9/2006 – 2/2007 USA (12)

			N treated (clev/other) Safety Eval	Primary Objective	Population	Control	Dose per protocol*	Follow-up (days)	Study Dates Sites
Other Trials (Phase I and II)			**554 (533 unique)**						
Perioperative HTN									
		Notes							
SH-SAD	0005		18 (14/14) (9 in Phase 2)	Postop Dose-HD response (Titrate to MAP) Concomitant beta-blocker	Cardiac surg	OL SNP	Maintain MAP 70-80 mmHg (both CLV and SNP) in Phase 1 (0.46 – 9.46 ug/kg/min) Phase 2 (DR), CLV 0.37 ug/kg/min 0.75 ug/kg/min 1.5 ug/kg/min 3.0 ug/kg/min (10 minute infusions)	none	1/1996 – 5/1996 Sweden (1)
SH-SAD	0003	BB allowed the morning of surgery; May have been insufficient washout of previous antiHTN med (d/c 5 min before randomization)	85 (83/2)	Dose ranging, Postop BP assessed at 10 min after a fixed infusion, HD response, PK, (MAP during infusion 65-105 mmHg – safety parameter; 1 dose adjustment allowed before study d/c)	Cardiac surg	Parallel Pbo	0.05 ug/kg/min 0.18 ug/kg/min 0.32 ug/kg/min 1.37 ug/kg/min 3.19 ug/kg/min 9.58 ug/kg/min Pbo – 1.37 ug/kg/min 122 minutes total including 12 min for titration Optional maintenance phase (MAP 70-95 mmHg) x 12 h	4-33 days, median 6 days	6/1996 – 3/1997 USA (6)

		Notes	N treated (clev/other) Safety Eval	Primary Objective	Population	Control	Dose per protocol*	Follow-up (days)	Study Dates Sites
Perioperative HTN (continued)									
SH-SAD	0006		18	dose titrate to MAP intraop PK pre-bypass and PK bypass (hypothermic)	Cardiac surgery (CABG)	OL Allowed SNP escape	Start 1.9 – 6.1 ug/kg/min (prebypass) 2.2-5.1 ug/kg/min (bypass); Max 16.8 ug/kg/min (prebypass), 8.2 ug/kg/min (bypass) 10 min constant infuion	4-7 days post-op visit	8/1996 – 1/1997 UK (1)
SH-SAD	0013	Metoprolol 50 mg x1 for those on BB	31 (16/15) 3 OL CLV	dose titrate to MAP 70-80 Vs. SNP postop BP control	Cardiac surgery (CABG)	DB, parallel SNP	Starting dose: 0.6 ug/kg/min CLV 0.5 ug/kg/min SNP Up to 3 h	4-7 days post-op visit	3/1997 – 9/1997 UK (2)
SH-SAD	0017		60 (29/31) 10 OL CLV	BP control intra- or postop; Titrate to effect	Cardiac surgery	DB, Pbo, Optional NTG	Start: 40 ug/min (based on 0.5 ug/kg/min, 80 kg person) Range: 16-640 ug/min Up to 12 h	30 days post-op visit	10/1997 – 4/1998 Sweden (5)
TMC-CLV	02-01		110 (49 / 51) 6 OL CLV 5 OL NTG	Vs. NTG for BP control and preservation of renal fxn Titrate to MAP	Cardiac surgery (CABG)	DB,	Start 0.2 ug/kg/min		

		Notes	N treated (clev/other) Safety Eval	Primary Objective	Population	Control	Dose per protocol*	Follow-up (days)	Study Dates Sites
Essential HTN									
SH-SAD	0004		13	Dose - BP Concomitant beta-blocker	Moderate to severe HTN	SB	Dose adjusted to maintain MAP decrease of 5, 10, 15% from bsl 0.06 – 0.17 ug/kg/min 0.12 – 0.63 ug/kg/min 0.21 – 0.83 ug/kg/min (1.1 – 2.9 h)	Day 2-5	11/1995 – 2/1996 Sweden (1)
SH-SAD	0010		21 (21/13)	PK CLV, enantiomers Dose rate – Cp Dose rate – BP tolerability	Moderate HTN	Pbo, SB 3-way X-over 5 arm	CLV 0.18 ug/kg/min 0.91 ug/kg/min 2.74 ug/kg/min 5.48 ug/kg/min Titration, 2 h infusion	Day 5 Patient visit	06/1996 – 10/1996 Sweden (1)
TMC-CLV	06-01		61 (48/13)	Tolerance Rebound PK ΔSBP72h	Mild-moderate HTN	Pbo, SB parallel	CLV Cohort 1: 2.0 mg/h 2: 4.0 mg/h 3: 8.0 mg/h 4: 16.0 mg/h Start at 2 mg/h, double every 3 min until target 72 hr infusion	Day 4 after infusion stopped	9/2006 – 2/1007 USA (3)

		Notes	N treated (clev/other) Safety Eval	Primary Objective	Population	Control	Dose per protocol*	Follow-up (days)	Study Dates Sites
Healthy									
SH-SAD	0001		46 (36/10)	Dose ranging Tolerance PK CLV and metabolite	Healthy males	Pbo, SB, X-over (3 day washout)	10 doses ranging from 0.06 ug/kg/min – 22 ug/kg/min 20 min infusions	Day 2-5 Patient visit	8/1995 – 9/1995 Sweden (1)
SH-SAD	0002	---	8	Mass balance CLV & metabolite H 152/81	Healthy males	no	1030 nmol/min containing 3.7 Mbq Actual dose: 5.5 – 6.8 ug/kg/min 60 min infusion	none	10/1995 – 11/1995 Sweden (1)
SH-SAD	0018	---	14	PK	Healthy males	OL	0.91 and 3.2 ug/kg/min x 24 h and 3.2 ug/kg/min x 20 min	2-5 days	3/1997 – 5/1997 Sweden (1)
TMC-CLV	05-01	QT	54 (41/54)	QT	healthy	SB,X-over moxi	3.2 ug/kg/min	7 days telephone	4/2006 – 9/2006

NTG=nitroglycerin, SNP=sodium nitroprusside, NIC=nicardipine, moxi=moxifloxacin
NR=non-randomized
SB=single-blind
Follow-up is listed as time after last study day
*All doses converted to ug/kg/min or ug/min if dosed in nmols.
DR=dose response, HD=hemodynamics

4.3 Review Strategy

I reviewed all 19 clinical trials. The efficacy data were examined within study but were also pooled for the two pivotal, placebo controlled studies (ESCAPE). More attention was given to studies that provided insight into dose response (DR) in hypertensives because most of the studies were titration to effect (usually to a MAP) studies (including the pivotal trials). The best studies for information on DR were study 06-01, a randomized, parallel, placebo controlled, 72 hour infusion study in hypertensives patients and study SH-SAD-0003, a randomized, parallel, placebo controlled, 122 minutes infusion study in cardiac surgery patients. Both studies did, however, include a period of titration before remaining on a continuous infusion.

I reviewed the safety data within study by reading the sponsor's description and the narratives and case report forms (CRFs) with more attention paid to the ECLIPSE studies (safety, active comparator studies) since they were the largest studies that also contained an independent committee to adjudicate the endpoints of death, MI, stroke, and renal dysfunction. An in-depth safety review was conducted of the sponsor's integrated safety datasets with extensive attention paid to death, hypotension, hypertension, afib, MI and stroke. Results were crosschecked with the sponsor's tables in the ISS.

This review was conducted jointly with Dr. John Lawrence (biostatistician). He reviewed the sponsor's efficacy analysis of the two pivotal trials and conducted additional analysis of the data to support efficacy. Regular communication was held with Dr. Chris Tornoe, the pharmacometric reviewer because of key questions related to exposure response (tolerance, rebound, onset, offset, and duration of effect) that were difficult to ascertain from the pivotal trials.

4.4 Data Quality and Integrity

The data quality and integrity seem acceptable.

The primary endpoint, the proportion of patients that did not require bailout therapy, was examined by site in the two major efficacy trials. ESCAPE-1 had 105 subjects (152 randomized) from 12 sites. Site 111 was selected because it had the most placebo-treated patients classified as bailouts and had no clevidipine-treated patients classified as bailouts (see table).

Table 5. Patients reaching primary endpoint by study-ESCAPE-1

Site #	101	102	103	104	105	107	109	111	112	114	115	116
Pbo (n)	5	0	6	3	10	3	3	7	2	9	1	3
Bailouts (n)	5	0	6	3	6	3	1	7	2	7	1	2
CLV (n)	7	1	7	3	10	1	2	5	3	11	0	3
Bailouts (n)	0	0	0	0	1	0	1	0	0	2	0	0

ESCAPE-2 has 110 subjects from 13 sites. Site 201 was selected because it had the most placebo-treated patients classified as bailouts and had only 1 out of 11 clevidipine-treated patients classified as bailouts.

Table 6. Patients reaching primary endpoint by study-ESCAPE-2

Site #	200	201	202	203	204	205	206	207	211	212	214	215	216
Pbo (n)	4	9	2	8	1	5	5	0	1	1	1	10	2
Bailouts (n)	3	9	1	8	1	4	1	0	1	0	1	8	2
CLV (n)	3	11	6	12	1	6	4	1	2	1	6	8	0
Bailouts (n)	0	1	0	1	0	1	0	0	0	0	0	2	0

DSI final review and letter dated 9 Nov 2007 and 25 Jan 2008 were used for this summary. DSI inspected site 111, Dr. Minkowitz in Houston, TX, on October 10, 2007 and site 201, Dr. Neil K. Singha, Huntington Memorial Hospital in Pasadena, CA, between October 3-11, 2007. Both sites adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. No significant deviations were noted and no FDA-483 was issued.

For site 111, all subjects' records were reviewed. CRFs corroborated with data listings. Adverse events, drug accountability records, and all regulatory records, including sponsor and monitor correspondence and IRB correspondence were reviewed. All informed consents were signed.

Details of the inspection at site 201 were not as extensively provided in their review. This is likely due to the deficiencies found during the inspection (thus, the bulk of the report). The field classified this as VAI because of certain protocol deviations that were directed by the sponsor. These included lack of reporting segmented and banded neutrophil counts, using Troponin I instead of CK MB (the hospital no longer used CKMB), and rounding the time of dose administration to the nearest minute (the CRF did not allow for half minute increments).

4.5 Compliance with Good Clinical Practices

The sponsor states that all studies were conducted with the ethical principles that have their origins in the Declaration of Helsinki, the ICH Good Clinical Practice guidelines or any local country GCP, whichever are the strictest. Study protocols, amendments, and informed consent were reviewed and approved by IRBs or Ethics Committees at each participating institution. Written informed consent was obtained from all patients. The DSI review discussed above, did not identify any significant protocol violations. There were protocol deviations in the six Phase III studies. These are all described by the Sponsor. Additionally, the reviewer found over 61 patients in the ESCAPE and ECLIPSE trials that were not initiated at the protocol stated dose of 0.4 ug/kg/min (See 6.1.3.2) Some patients were started on ten times the initial recommended dose.

4.6 Financial Disclosures

Appropriate financial disclosures were submitted for The Medicine Company studies. The sponsor certified that 140 investigators had no significant financial arrangements (form 3454). A significant payment was made to [redacted] totaling $654,239 from 2003 - 2007(Form 3455). He enrolled 10 patients into [redacted] (site [redacted]) and 1 patient into [redacted] (site [redacted]). The reviewer checked the [redacted] data for site [redacted] Although 10

patients were enrolled at this site, only 5 received treatment (3 placebo and 2 clevidipine). BP data were only available for 4 of these patients. It is unlikely that 4 patients will influence the results and the mean percent change in BP. A crude (combining placebo and clevidipine) look at the mean percent decrease in BP (baseline adjusted) in all 4 subjects was -12.6/-16.3 mm Hg. The mean percent decrease in BP (baseline adjusted) for all other sites was -14.0/-12.6 mm Hg.

Financial disclosures for the Astra Zeneca conducted studies were not submitted.

The paper financial disclosure forms were cross checked with the SAS datasets in the ISS, "d_ex.xpt", "d_ae.xpt" and the ISE "d_ex.xpt". Sites with financial disclosures but no patient exposure information were checked for withdrawals. These included study 03-03, site 358, and study 03-04, sites 411 and 438. Three patients did not meet post-randomization criteria and 1 did not meet pre-randomization criteria.

5 CLINICAL PHARMACOLOGY

This summary is based on the reviewer's assessment of the clinical pharmacology studies and the draft Pharmacometrics review by Dr. Christopher Tornoe dated 28 January 2008 with minor modifications (dated 08 February 2008). A draft Clinical Pharmacology review was not available at the time this review was being finalized. The reader should refer to the final Clinical Pharmacology review and Pharmacometrics review (March 2008) for complete information.

5.1 Pharmacokinetics

Clevidipine is completely and rapidly metabolized with its major metabolite further metabolized and eliminated by the kidney. Clevidipine is metabolized by hydrolysis in blood and tissues by non-specific carboxyl esterases in the blood, vascular endothelium and extravascular tissue to a pharmacologically inactive carboxylic acid (metabolite M1 or H152/81). M1 is further metabolized by glucuronidation or oxidation to the corresponding pyridine derivative and then excreted by the kidney. This metabolism differs from most other dihydropyridines (except for amlodipine), which are metabolized by the cytochrome P450 3A4 system and undergo saturable first pass in the liver.

Clevidipine and M1 are unlikely to cause cytochrome (CYP) P450 interactions. The concentrations of clevidipine and M1 that induce or inhibit P450 isoforms were at least 10 times higher than the highest clevidipine or metabolite concentration in clinical use (100 nmol/L). The magnitude of induction/inhibition was also less than the positive control.

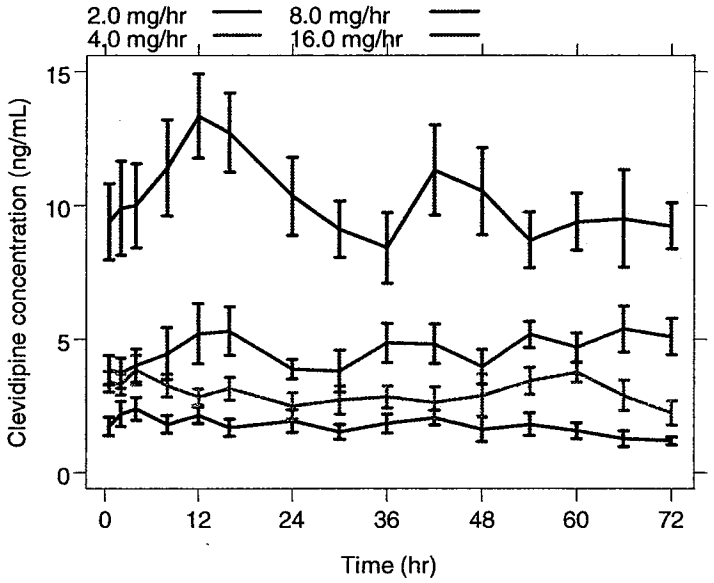
Each enantiomer shows similar PK in patients with essential hypertension (study 0010).

Clevidipine exhibits high plasma protein binding (99.5%) and a volume of distribution of 313 L, indicating extensive tissue distribution.

Clearance of clevidipine is extremely rapid (1500 L/hr). Clevidipine clearance was found to be influenced by body weight, body temperature, time since start of infusion, gender, and patient

population. There was also an indication of time dependence with up to a 20% increase over the 72 hour infusion (see figure).

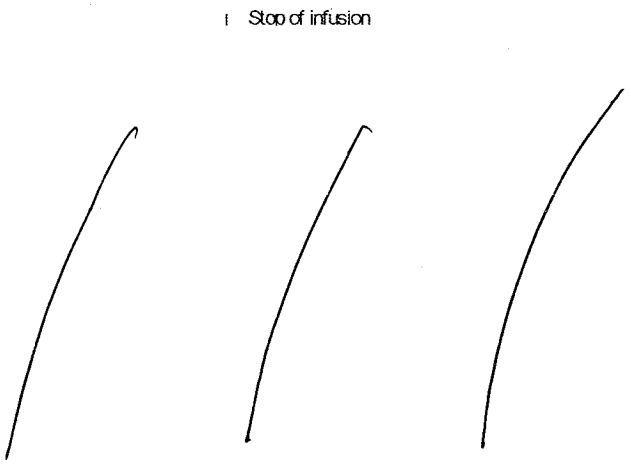
Figure 3. Clevidipine concentrations over 72 hours (mean±SE), TMC-CLV-06-01



Taken from PM review, pg 19 of 58

Females had 25% lower clearance compared to males. Severe hypertensives had 30% lower clearance compared to mild-moderate hypertensives. Clearance was also slower in hypothermia (during bypass) (0.03 L/min/kg) compared to normothermia (pre-bypass) (0.06 L/min/kg) (see figure).

Figure 4. Clevidipine concentration pre-bypass (normothermic) and bypass (hypothermic)



Taken from Sponsor's Summary of Clin Pharm, Figure 29
Representative patient, dose rate pf 2.05 ug/kg/min (~9.8 mg/hr)

The identified clearance covariates are not expected to have a significant clinical impact since clevidipine has a very short half-life and is titrated to effect. Dr. Tornoe recommends no dose adjustments based on significant covariates.

Consistent with the rapid clearance is a short half-life, with a distribution phase (α) of 2-3 minutes, and an elimination phase (β) of approximately 1 hour. All PK parameters are based on Dr. Tornoe's population PK analysis in hypertensives and does not differ from the sponsor's population PK analysis. However the half-life estimates are somewhat longer or could be consistent with the sponsor's depending on what study is used for comparison. According to the sponsor, the most accurate assessment of half-life was made in SH-SAD-0018, a study in healthy volunteers. In this study, the venous blood initial half-life (distribution) was less than 2 minutes and the terminal half-life was around 1 hour (consistent with the Agency population PK). The sponsor _____ for the proposed package insert. There will have to be discussions with Clinical Pharmacology to decide on the most appropriate labeling.

A majority (83%) of the radiolabeled dose is excreted in urine (major) and feces (minor) as inactive metabolite. More than 90% of recovered radioactivity is excreted within the first 72 hours.

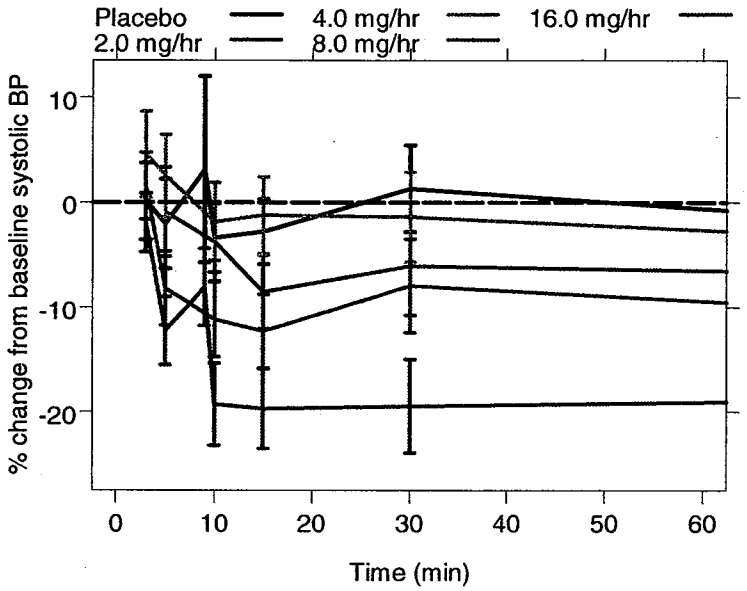
In-vivo drug–drug interactions were not done due to the short term administration of clevidipine.

5.2 Pharmacodynamics

5.2.1 Onset

The time to maximal onset of effect is about 10-15 minutes after the start of the infusion. The figure below shows data from study 06-01, the 72 hour constant infusion study. It should be noted that doses greater then 2 mg/hr were force titrated by doubling the initial rate of 2 mg/h every 3 minutes until the target dose was reached. The green line below (2 mg/h) depicts the only dose that was not force titrated. It shows that the maximal effect occurred around 15 minutes after the start of the infusion, although there is a lot of variability (error bars depict the 90% CI). The figure shows a lack of a dose response for the first two infusion rates as the 4 mg/h infusion has less of a mean effect than the 2 mg/h infusion.

Figure 5. Change from baseline SBP (mean, 90% CI)), TMC-CLV-06-01



Taken from PM review, pg 30 of 58

Another study that provides insight into the onset of effect is study SH-SAD-0003. This was a placebo-controlled, parallel study that used an initial fixed dose infusion for 10 minutes before starting the "constant infusion phase". The figures shown next are from the time after the start of the fixed dose of 10 minutes (BP during the 10 minute fixed dose infusion were not reported). Nevertheless, one would expect to see a leveling out of effect around the first time points based on the study 06-01 data.

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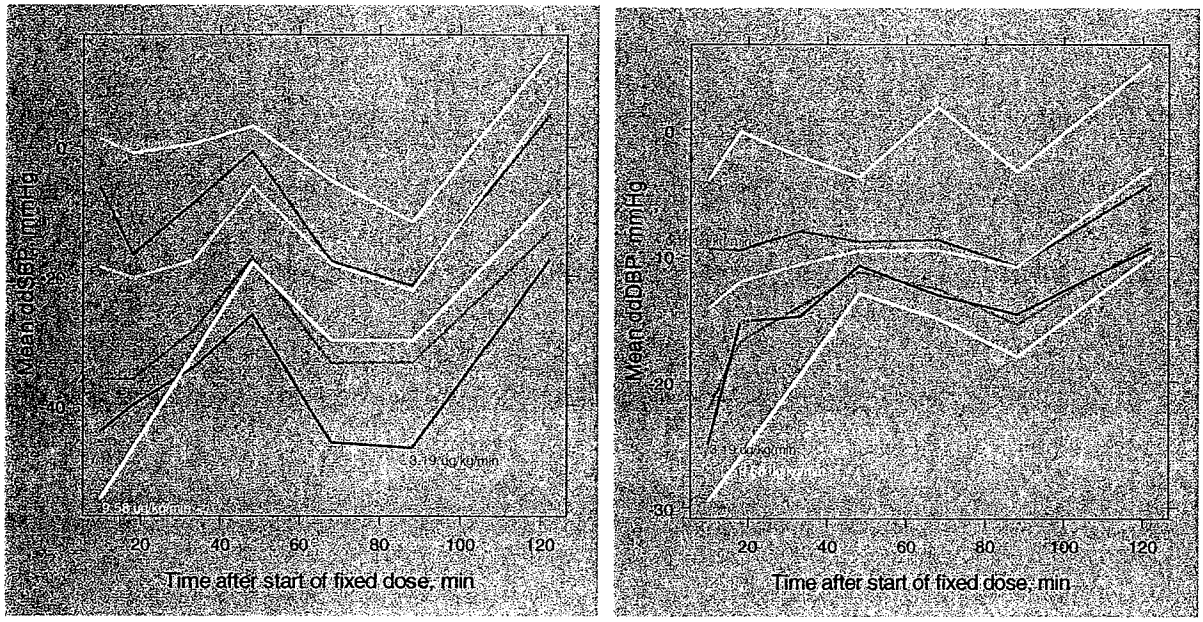
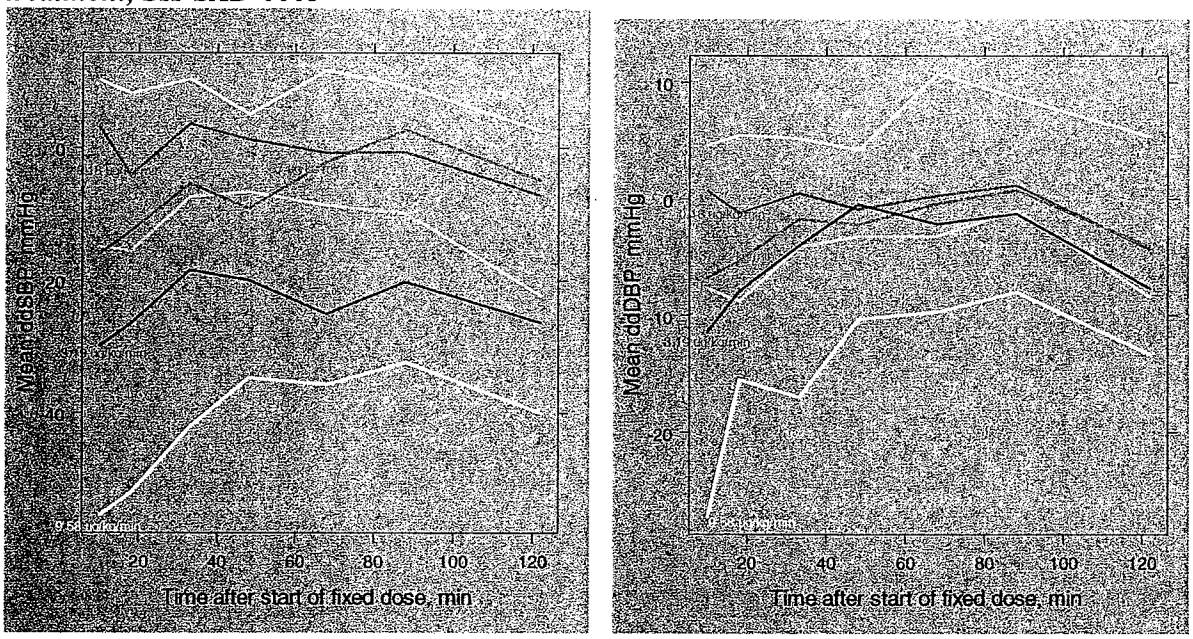
Figure 6. Effect on BP after the fixed dosed infusion of 10 minutes – actual treatment, SH-SAD-0003



However, there seems to be a diurnal pattern in the BP response over time. This effect is somewhat lessened when examined by randomized dose.

Figure 7. Effect on BP after the fixed dosed infusion of 10 minutes – randomized treatment, SH-SAD-0003

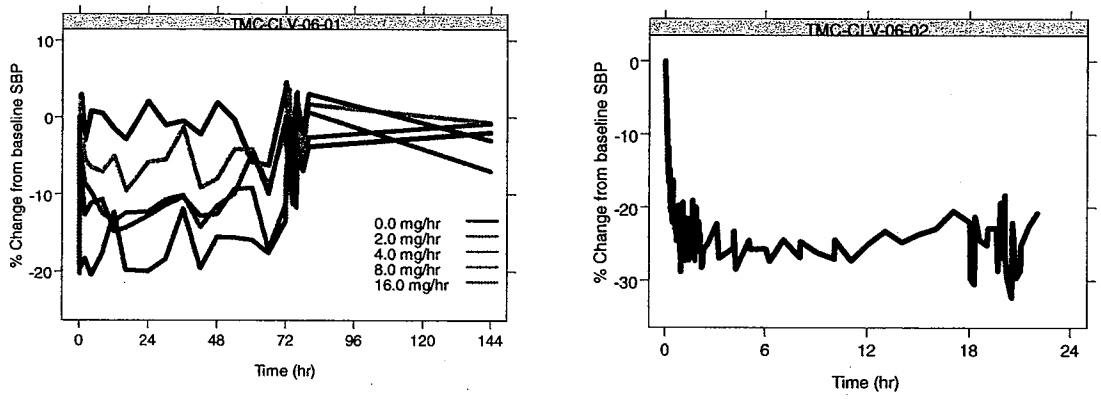


This effect is also seen in Study 06-01 (see figure that follows) (also noted by Dr. Tornoe).

5.2.2 Duration / Tolerance

The duration of SBP effect appears to be the duration of clevidipine infusion.

Figure 8. Effect on SBP during continuous infusion), TMC-CLV-06-01 and 06-02



Mean percent change from baseline systolic blood pressure time profiles for mild to moderate hypertension patients following 72 hours constant clevidipine infusion (left) and 30 minutes forced titration followed by target SBP titration in patients with severe hypertension (right).

Taken from PM review, pg 30 of 58

As mentioned in the previous section, there appears to be a diurnal effect on BP or clevidipine is unable to blunt the natural diurnal effect of BP. One would expect the maximal effect to coincide with clevidipine concentrations, however, almost the exact opposite was found for study 06-01. Compare Figure 3 and Figure 8 to see that when clevidipine concentrations are at peak, SBP effect is the smallest.

There does not appear to be any tolerance development since no delay (hysteresis) was observed between clevidipine concentration and percent change from baseline SBP with or without placebo adjustment (see figure).

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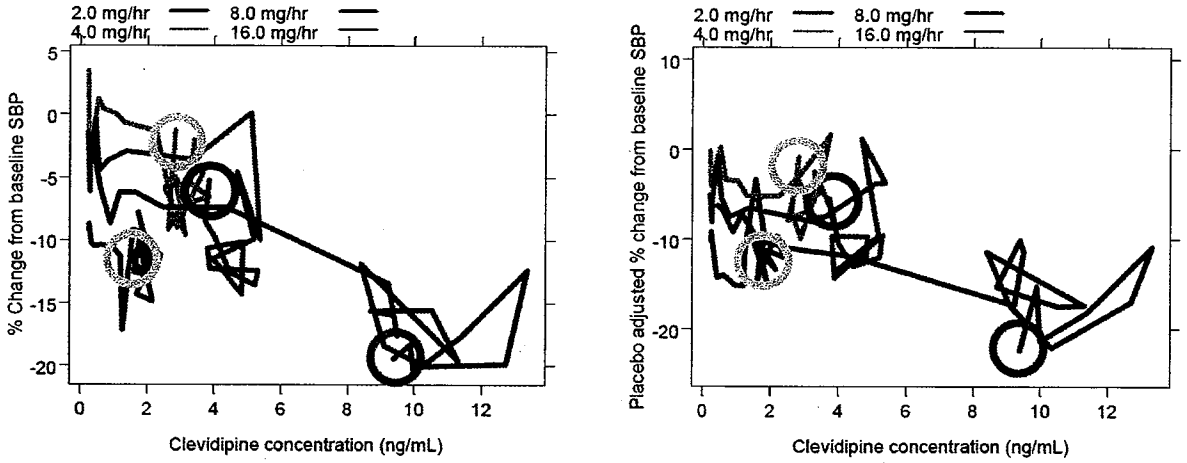
ON ORIGINAL

Figure 9. Absence of hysteresis between clevidipine concentration and change in SBP



Relationship between time-matched mean percent change in SBP from baseline (left) and placebo-adjusted (right) and the mean clevidipine concentration over the 72 hour treatment period through 60 minutes post study drug infusion connected by lines in chronological order for study TMC-CLV-06-01 (see appendix 10.4 for mean ±SE plots). The circles indicate the first time point with PK and SBP measurement.

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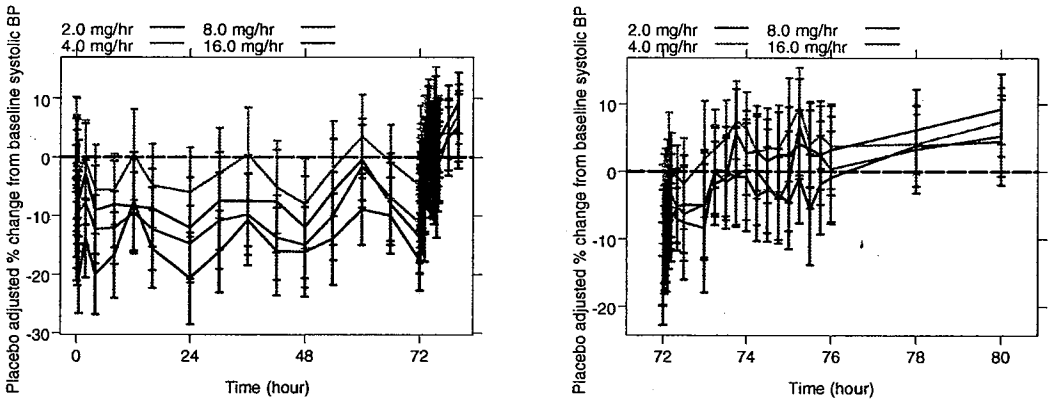
5.2.3 Offset

The rapid clearance of clevidipine and direct effect on SBP result in a fast offset of SBP effect. In most patients, full recovery to baseline SBP is achieved in 5-15 minutes after end of clevidipine infusion.

5.2.4 Rebound

There is evidence of rebound after the end of the clevidipine infusion. The mean placebo-adjusted percent change from baseline SBP at 8 hours post infusion (hour 80) for the 4 and 16 mg/hr cohorts in TMC-CLV-06-01 were 7.4 (90% CI 2.3-12.5) and 9.3 (90% CI 4.1-14.5) (see orange and red lines in right graph). This corresponds to a rebound of 11 and 14 mm Hg in absolute systolic blood pressure for a patient with the mean baseline SBP of 150 mm Hg.

Figure 10. Rebound, TMC-CLV- 06-01



Mean (90% CI) placebo-adjusted percent change from baseline systolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CLV-06-01.

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5.3 Exposure-Response Relationships

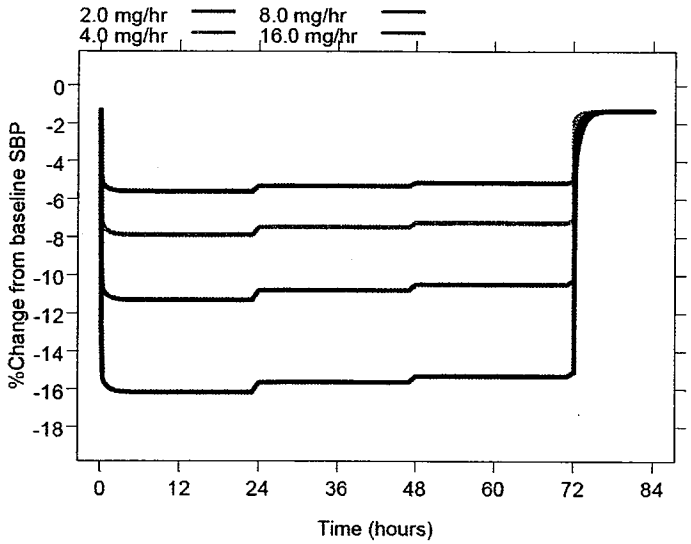
Most of these were discussed in Section 5.2 Pharmacodynamics.

It is noted that Dr. Tornoe's population PK/PD analysis was based on data from studies 06-01 (randomized, single-blind, placebo-controlled, parallel, force titration, 72 hour infusion in mild to moderate hypertensives) and 06-02 (uncontrolled, open-label, titrate to effect, then dose maintained for 18 to 96 hours in severe hypertensives). Details of these studies are found at these links or in the pharmacometric review.

Dr. Tornoe's population PK/SBP analysis used study 06-01 (mild to moderate hypertensives, rich PK data) for model building and the PK data in study 06-02 (severe hypertensives, sparse PK data (n=30)) for external validation. The relationship between clevidipine concentration and change from baseline SBP was best described with direct effect Emax model. The mean maximal SBP change from baseline was -25 %. This would correspond to a 40 mmHg decrease in SBP for a patient with a baseline SBP of 150 mmHg. The concentration that produced half of that maximal effect was 7.1 ng/mL, that is approximately 10-12 mg/hr. The mean EC50 estimate was not very precise (SE of ~50%). This translates into an EC50 that could be 0 or 14 ng/mL. Possible reasons for this imprecision include the small number of subjects and the diurnal effects that were not modeled.

The population predicted percent change from baseline is shown in the following figure.

Figure 11. Population predicted % change from baseline SBP, PK/PD model



Severe hypertensives were more sensitive to clevidipine as demonstrated by a lower EC50 of ~ 1-2 ng/mL; Emax was similar to mild to moderate hypertensives. It is unclear why there appears to be a difference in BP response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indicated being sought is [redacted]) when the use of oral therapy is not feasible or not desirable.

6.1.1 Methods

The six studies included in the Sponsor's ISE are listed first (and grayed) in Table 4. They include two pivotal, randomized, double-blind, placebo-controlled studies in perioperative patients (ESCAPE-1 and -2), three randomized, active-controlled, safety studies in perioperative patients (ECLIPSE-NTG, -SNP, -NIC) and one uncontrolled, open-label study in severe hypertensive patients (VELOCITY). These studies comprised a total of 1,846 patients, of which 992 were randomized to clevidipine, 100 to placebo, and 754 to active control (278 to nitroglycerin (NTG), 283 to sodium nitroprusside (SNP), and 193 to nicardipine (NIC)).

6.1.2 General Discussion of Endpoints

The primary endpoint in the ESCAPE studies was the proportion of patients who bailed out in the modified intent to treat population (mITT, defined in Section 6.1.3.5). Bailout was defined as the premature discontinuation of study drug infusion by 30 minutes after the start of the infusion. The Division accepted and agreed on this endpoint in March 2003. The investigator was allowed to bailout for any reason and at any time during the first 30 minutes of the study drug infusion. Reasons for bailout were categorized into:

- lack of efficacy (no change or an increase in SBP by an investigator chosen time whereby it was unethical to continue blinded treatment),
- safety (occurrence of TEAE that necessitated discontinuation of drug and initiation of an alternate antihypertensive), and
- treatment failure (not attaining a 15% decrease in SBP by 30 minutes).

Secondary endpoints of ESCAPE included:

- Time to target SBP lowering, defined as a 15% reduction in SBP from baseline. Patients never reaching this endpoint were censored at the time of permanent stop of drug, initiation of an alternative antihypertensive treatment or last non-missing measurement of SBP within one hour following study drug initiation. Treatment comparisons were assessed by the log-rank test. This endpoint was pooled for the ESCAPE studies.

The following were secondary efficacy endpoints, but were not pooled for analysis by the sponsor, nor were they discussed in the Sponsor's ISE.

- Change in MAP from baseline and the incidence of bailout by causality

The ECLIPSE trials were designed to assess safety. As such, all primary endpoints were safety related. The drug effect on BP was a secondary endpoint and was analyzed as the AUC of SBP outside of a predefined range, AUC_{SBP-D} (65-135 mmHg intraoperatively and 75-145 mmHg pre- and post-operatively). The AUC analysis, while not clinically intuitive or informative, provides a quantitative number of the magnitude and duration of SBP excursions. Other secondary efficacy endpoints included the use of alternative IV antihypertensive agents for BP control. Since these studies were not designed to assess efficacy (no apriori defined efficacy endpoint), there were no definitions of HTN to start medication (initiation was at the sole discretion of PI), BP were recorded infrequently (making reviewer assessment of dosing difficult, see Section 6.1.3.3) and all were titration to effect studies (thus no additional information gained on raw dose response) with no placebo control, the reviewer did not include them in her assessment of efficacy. Since the Sponsor included the ECLIPSE studies in its ISE, the sponsor's secondary analysis results will be presented.

VELOCITY was the sole Phase III trial in patients with severe hypertension. There were two co-primary endpoints, one for safety and one for efficacy. The efficacy endpoint was the percentage of patients who reached their patient specific target SBP range within 30 minutes of initiating the infusion. The amount of BP reduction was not prespecified by the sponsor and varied from patient to patient, but was to be between 20-40 mmHg. However, the sponsor states that it was expected that the investigator determine a target SBP reduction of the usual and

customary ~ 15%. Time to attainment of 30 minute SBP target was a secondary efficacy endpoint. Since this was the only large study in severe hypertension, the reviewer examined the efficacy results (separately from ESCAPE because of the different patient population). (Study SH-SAD-0004 was a small Phase I study that included moderate to severe hypertensives.)

6.1.3 Study Design

The ESCAPE studies (Efficacy study of clevidipine assessing its preoperative (ESCAPE-1) / postoperative (ESCAPE-2) antihypertensive effect in cardiac surgery) were randomized, double-blind, placebo-controlled, parallel, multicenter, short infusion (30 minutes to 1 hour) studies in cardiac surgery patients. These two studies are the best studies for the assessment of effectiveness. They were large, randomized, placebo controlled, double-blinded with a predefined statistical analysis plan (SAP), however there was no endpoint committee for adjudication, and the duration of drug infusion was short. The ESCAPE studies were conducted in three periods: pretreatment (up to 14 days prior to study drug administration), treatment (start of study drug administration up to bailout, or up to the point of induction of anesthesia, or for a maximum duration of one hour after study drug initiation), and the follow-up period (from permanent stop of study drug administration to hospital discharge or seven days, whichever occurred first). Follow-up was performed at 24 hours after SDA and at hospital discharge or seven days (whichever occurred first).

The ECLIPSE studies (Evaluation of clevidipine in the perioperative treatment of hypertension assessing safety events) were randomized, parallel, open label, active comparator studies in cardiac surgery patients also. The three active comparators were NTG and SNP given perioperatively (pre and during) and NIC given postoperatively for a desired BP and continued until discharge from the ICU. As previously mentioned, these studies were conducted primarily for safety information. Conclusions based on efficacy are difficult for reasons mentioned in Section 6.1.2. Follow-up was obtained for all patients whether or not they received their assigned treatment or discontinued study drug. Patients not meeting the postrandomization criteria were not subjected to interventions beyond standard of care and were not followed. The Day of operation was designated as Day 0. Assessments were conducted until discharge from the hospital or Day 7, whichever occurred first. The follow-up period began from ICU discharge to Day 30.

For the ESCAPE and ECLIPSE studies, randomization was stratified by site in blocks of four (in the order that the patients qualified) and occurred on the day of surgery or up to 24 h prior to the scheduled surgery. Treatment groups were studied concurrently.

VELOCITY (Evaluation of the effect of ultrashort-acting clevidipine in the treatment of patients with severe hypertension) was an open-label, non-controlled study in patients with severe hypertension. Enrollment was to continue until a minimum of 100 patients received ≥ 18 hours of clevidipine infusion, including a minimum of 50 patients with acute or chronic end organ injury. Patients were expected to reach target SBP within 30 minutes. If this did not happen, an alternate IV antihypertensive was allowed +/- clevidipine. Patients receiving an alternate IV antihypertensive with clevidipine continued in the study. After 30 minutes, the investigator could alter the desired target range. Clevidipine dosing duration was from 18 to 96 hours.

Patients transitioned to oral therapy as necessary approximately 1 hour prior to the anticipated cessation of clevidipine infusion. Transition was successful if the patient's BP was within a desirable range at 6 hours after cessation of clevidipine. A subset of patients had sparse PK sampling. Patients were assessed during the clevidipine titration phase, throughout maintenance dosing, and until 6 hours after clevidipine infusion was discontinued. A follow-up phone call was made at 7 days after initiation of clevidipine infusion to determine if any SAEs had occurred.

6.1.3.1 Population (Inclusion/Exclusion)

For the ESCAPE and ECLIPSE studies eligible patients included those with a recent history of HTN or who were hypertensive on admission (see study title for perioperative or postoperative hypertension for study inclusion) and were scheduled for cardiac surgery. The perioperative period was defined as the period immediately before, during, and after surgery until discharge from the ICU. The elective cardiac surgery included CABG, off-pump coronary artery bypass (OPCAB), or minimally invasive direct coronary artery bypass (MIDCAB) surgery and/or valve replacement/repair. Patients were excluded for soybean oil or egg lecithin allergy, cerebral vascular accident (CVA) within 3 months, women of child-bearing potential, pre-existing permanent ventricular pacing, and left bundle branch block (LBBB) (for ESCAPE).

Patients had to meet the post randomization criteria to continue in the study. For ESCAPE-1 that meant a preoperative SBP ≥ 160 mmHg after insertion of the arterial line; and investigator intention to lower SBP by at least 15% from baseline. Since ESCAPE-2 was postoperative, there were more restrictions for inclusion, including an expected survival beyond 24 hours post surgery, no surgical complications or conditions, present or anticipated, that would preclude the subject from a double-blind, placebo-controlled trial, a postoperative SBP ≥ 140 mmHg within 4 hours of arrival in the postoperative setting, and the same investigator intent to lower SBP as in ESCAPE-1.

The ECLIPSE trials did not have prespecified inclusion BPs, merely the postrandomization criteria was "hypertension as determined by the investigator". Since ECLIPSE-NIC was postoperative, additional inclusion restrictions included expected survival beyond 24 hours and no surgical complications or conditions.

The VELOCITY trial enrolled patients with a SBP > 180 mmHg and/or DBP > 115 mmHg assessed on two successive occasions 15 minutes apart at baseline. One of the qualifying occasions was the day prior to study drug infusion. Patients were excluded if they might be intolerable to IV antihypertensives for a minimum of 18 hours, had known aortic dissection, took an antihypertensive within 2 hours of clevidipine, had a positive pregnancy test, was allergic to soybean oil or egg lecithin, had liver failure or cirrhosis, had severe hypertension known to be precipitated by use of, or withdrawal from alcohol or illicit drugs.

6.1.3.2 Dose

The adequacy of the dose finding for Phase III is discussed in Section 8.1.

The dose titration instructions were essentially the same in both the ESCAPE and ECLIPSE studies. Clevidipine infusion started at 0.4 ug/kg/min (approximately 2 mg/hr), titrated upwards, as tolerated, in doubling increment every 90 seconds up to an infusion rate of 3.2 ug/kg/min (approximately 16 mg/hr), in order to achieve the desired BP lowering effect. Rates above 3.2 ug/kg/min were titrated in increments of 1.5 ug/kg/min. The maximum clevidipine infusion rate was 8.0 ug/kg/min.

The reviewer transformed the initial infusion (weight based) into a mg/hr infusion since the sponsor seeks dosing instructions irrespective of weight. The table below shows the initial dose in patients. The mean actual dose (mg/h) and 90% CI indicate that most patients did start around a dose of 2 mg/hr.

Table 7. Initial dose in mg/h when protocol stated initial dose is 0.4 ug/kg/min

	Dose per protocol ug/kg/min	Actual mean dose ug/kg/min	90% CI ug/kg/min	Min ug/kg/min	Max ug/kg/min	Actual mean dose mg/h	90% CI mg/h	Min mg/h	Max mg/h
ESCAPE	**0.4**	**0.40**	**0.40 – 0.41**	**0.24**	**0.80**	**2.07**	**1.99 – 2.15**	**1.13**	**4.85**
ECLIPSE	**0.4**	**0.49**	**0.45 – 0.53**	**0.008**	**15.28**	**2.65**	**2.35 – 2.96**	**0.05**	**125**

Dataset used: d_ex in ISE
Min=minimum, max=maximum

There were 61 patients with initial infusion rates of 0.5 ug/kg/min or higher; one (ID TMC-CLV-03-01_00112_00004) from ESCAPE (dose of 0.80 ug/kg/min); the rest were in the ECLIPSE trials (See Table 8). It is unclear why there were patients with very high initial starting doses. One subject (ID TMC-CLV-03-04_00407_00006) was started on 15.28 ug/kg/min or 125 mg/h. This patient received a bolus dose.

Table 8. Subjects with dose initiated at ≥0.5 ug/kg/min, ECLIPSE

Actual initial dose range (ug/kg/min)	Number subj
0.5 < 0.6	**8**
0.6 < 0.7	**1**
0.7 < 0.8	**10**
0.8 < 0.9	**15**
0.9 < 1.0	**2**
1 < 1.5	**3**
1.5 < 2	**11**
2 < 3	**1**
3 < 4	**3**
4 ≤ 5	**5**
> 5	**1**

Dataset used: d_ex.xpt in ISE

After the reviewer noted the protocol deviations to the sponsor, the sponsor admitted to not realizing the protocol deviation until I pointed it out to them. Their explanations are as follows:

In ESCAPE, the starting dose discrepancy for patient #