Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Clevidipine

Proprietary Product Name: Cleviprex

Sponsor: Kendle Australia Pty Ltd

June 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	12 April 2010
Active ingredient(s):	Clevidipine
Product Name(s):	Cleviprex
Sponsor's Name and Address:	Kendle Australia Pty Ltd PO Box 202 Oakleigh Vic 3166
Dose form(s):	Injectable emulsion
Strength(s):	25 mg in 50 mL and 50 mg in 100 mL
Container(s):	Sterile, single-use, pre-mixed 50 mL and 100 mL glass vials.
Pack size(s):	Cleviprex is supplied in single vials inside a carton. Each pack includes 10 cartons containing single-use vials.
Approved Therapeutic use:	Cleviprex is indicated for the short term treatment of hypertension when oral therapy is not feasible or desirable.
Route(s) of administration:	Intravenous infusion
Dosage:	Individualised to patient. In clinical trials, most patients were treated with doses of 4 to 6 mg/hour.
ARTG Numbers:	156137, 156138

Product Background

Cleviprex (clevidipine) is a new chemical entity belonging to the dihydropyridine class of calcium channel blockers that reduces mean arterial blood pressure by decreasing systemic vascular resistance. It is indicated for the reduction of blood pressure when rapid and predictable control is desired. The intravenous infusion of Cleviprex is initiated at 1-2 mg/h; the dose may be doubled every 90 seconds. Titration should be continued until the desired target blood pressure is achieved. The desired therapeutic response for most patients occurs at doses of 4 to 6 mg/h. In clinical studies most patients were treated with maximum doses of 16 mg/h or less. However, dosage has to be individualised depending on the blood pressure to be obtained and the response of the patient. It is administered by syringe or volumetric pump for patients requiring rapid blood pressure reduction when oral therapy is not feasible or desirable. It has been evaluated in clinical trials in durations up to 72 hours.

Regulatory Status

A similar application to the current Australian submission has been approved in USA on 2 July 2007 for the indication:

Cleviprex is a dihydropyridine calcium channel blocker indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable.

An application has also been approved in New Zealand on 31 July 2009 for the indication:

Cleviprex is indicated for the reduction of blood pressure when rapid and predictable control is desired.

An application for the same indication has been submitted and is under evaluation in the European Union (EU), Canada and Switzerland.

Product Information

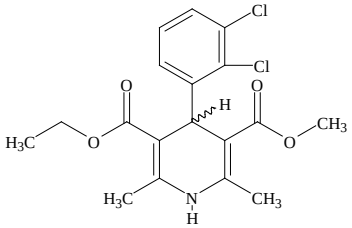
The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

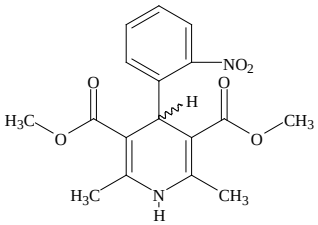
Drug Substance (active ingredient)

Structure

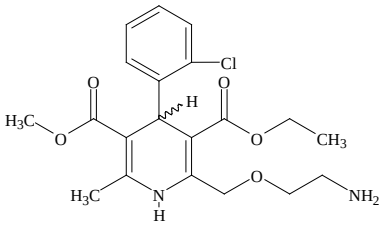
Clevidipine butyrate is a new chemical entity which is presented as a racemic mixture of two enantiomers. It is related to other dihydropyridines and in particular felodipine. The structures are shown below:



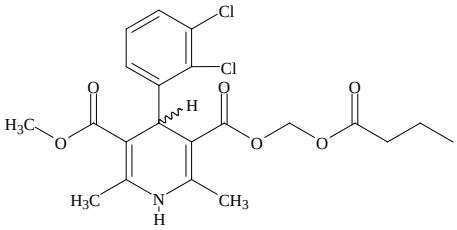
Felodipine



Nifedipine



Amlodipine



clevidipine butyrate

3-O-(butanoyloxymethyl)-5-O-methyl-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Formula = $C_{21}H_{23}Cl_2NO_6$ MW = 456.32

CAS No. = [167221-71-8] (racemate)

specific rotation = 0° melting point 138°C

aqueous solubility = 0.0001 mg/mL (0.00001 %w/v): practically insoluble

Clevidipine butyrate is a calcium channel blocker. It is rapidly distributed and metabolised. The metabolites are not active.

Manufacture

This substance is manufactured by chemical synthesis.

Physical and Chemical Properties

The drug substance is a white to off-white crystalline powder. Two polymorphic forms have been found and the drug substance obtained is >95% Form A. However, as the drug

substance is dissolved during the manufacture of the injectable emulsion, this is not critical parameter and neither is particle size distribution.

It is practically insoluble in water and aqueous buffers solution. Consequently, it is formulated as a soya oil emulsion.

Specifications

The specifications of clevidipine butyrate drug substance include satisfactory limits for assay (98.0-102.0%) and related substances (including an acceptable limit for the synthetic impurities chloromethyl butyrate and acrylonitrile).[1] The residual solvent limits were at or below limits allowed by ICH guidance.

Stability

The substance exhibits good stability and the real time data submitted support a retest period of 3 years when stored below 25°C.

Drug Product

Manufacture

The drug product is to be manufactured by Hospira Inc. in Clayton, North Carolina, USA. Due to the extremely low aqueous solubility of clevidipine butyrate, the products are an oil-in-water emulsion with the drug substance dissolved in the oil droplets.

- An aqueous phase is prepared by the dissolution of glycerol in hot (~75°C) Water for Injections.
- An oil phase is prepared by the dissolution of clevidipine butyrate in hot (~75°C) soya oil and the subsequent addition of egg lecithin (as an emulsifier).
- The two phases are mixed, pH adjusted (to ~pH 9.6) and homogenised to give a fine particle size emulsion.
- After cooling and filling under nitrogen, the final product is terminally sterilised by steam.

Specifications

Release and expiry specifications are identical apart from assay and pH.

Three expiry limits for degradants are above the ICH qualification threshold of 0.2%. This was referred to the Medicines Toxicology Evaluation Section (MTES) of the TGA.

Release limits for degradants were accepted.

The specifications do not include limits for free fatty acids or lysolecithin which are formed by the degradation of the egg phospholipids. Finally there is a limit for lysophosphatidyl choline (LPC), formed by the degradation of phosphatidyl choline which is present in the egg lecithin. This material has been associated with the onset of haemolytic anaemia, but MTES advised that this limit is acceptable.

The Microbiology Section of the Office of Laboratories and Scientific Services (OLSS) of the TGA found aspects relating to sterility acceptable and the proposed vials were acceptable

[1] The Medicines Toxicology Evaluation Section (MTES) advised that this limit for these potentially genotoxic impurities was qualified

with respect to container safety.[2] Further, the animal origins of the egg lecithin were acceptable.

Stability

Stability data was provided to support the proposed shelf life of 26 months when stored between 2-8ºC in the glass vials. The product may be removed from the refrigerator and stored at 25°C for 2 months during the shelf life, but it should not be returned to the refrigerator. The storage conditions 'do not freeze' and 'protect from light' also apply.

Bioavailability

The sponsor did not submit any bioavailability studies. It claimed that it was not possible to determine the absolute bioavailability compared to an aqueous solution due to the low solubility of clevidipine butyrate in water and in ethanol. It further argued that administration of the drug intravenously ensures that the entire dose enters the systemic circulation and that there is little potential of the emulsion formulation giving a precipitate or depot formation during use. This was accepted.

Consideration by PSC

This application was presented to the 127th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) in July 2009 where no objections were raised in relation to chemistry, quality control or bioavailability. However, the PSC considered that 'the PI should be amended to include statements in relation to whether this product can be: administered in the same line as other drug products; and diluted with commonly used parenteral solutions prior to administration'. The PI was amended to disallow any such use.

Quality Summary and Conclusions

Approval of this submission was recommended with respect to chemistry, quality control and bioavailability.

III. Nonclinical Findings

Introduction

The critical studies examining repeat-dose toxicity, genotoxicity, and teratogenicity were performed according to Good Laboratory Practice (GLP) standards. Nevertheless, the TGA evaluator agreed with the FDA assessment (NDA 22-156) that the interpretation of the general toxicology of clevidipine was impeded by the use of Intralipid as a vehicle: the vehicle alone caused body weight, clinical chemistry and histopathological changes in line with its lipid nature.[3] In some cases Intralipid also increased the apparent treatment-related effects of clevidipine. Moreover, several toxicology studies were either partially or fully compromised by poor animal husbandry whereby sepsis, keratitis, catheter closures and overall poor survival were observed.

Pharmacology

Primary pharmacodynamics

Rationale

[2] Although there is potential for the plasticiser MBETNP to leach from the vial stoppers, MTES did not consider the potential levels a risk to patient health

[3] FDA: Pharmacology Review(s): Center for Drug Evaluation and Research NDA 22-156.

Hypertension occurs in a significant fraction of patients undergoing cardiovascular surgery and is known to increase the risk of major surgical complications. While various antihypertensive drugs have been used to counteract this problem, such drugs can have drawbacks such as lack of selectivity for arteriolar vessels and difficulty of precisely regulating their effect on blood pressure (BP). Clevidipine is a dihydropyridine that inhibits transmembrane calcium influx through voltage-dependent L-type calcium channels in muscle cells of heart and blood vessels. This inhibition decreases muscle contraction and can lead to a drop in BP. Clevidipine was developed as an antihypertensive that combines high selectivity for vascular versus myocardial smooth muscle and rapid loss of activity (thus allowing precise titration of its antihypertensive effect).

In vitro studies

In vitro testing using rat neuronal cell cultures showed that clevidipine inhibited calcium influx induced by potassium. Clevidipine's inhibitory action was about 5-fold less potent than that of felodipine (a closely related antihypertensive agent). The vascular:myocardial selectivity ratio was about 50 in rat cell culture models.

In vivo studies

The intra-species potency of clevidipine to reduce arterial blood pressure was shown by the significant reduction in arterial blood pressure in rats at 50 nmol/kg, which is 100 times lower than the No Observable Adverse Effect Level (NOAEL) in the 4 week rat study. The dose of clevidipine required to reduce arterial BP by 20% was shown to be 5-times greater in normotensive than in spontaneously hypertensive (SH) rats and 10-times greater in conscious than in anaesthetised rats. The time for recovery of BP from 30% to 10% below basal pressure was compared in anaesthetised hypertensive rats that had been dosed with one of various antihypertensive agents. The recovery time for clevidipine (2±1 minutes) was similar to glyceryltrinitrate (4±3 minutes), longer than nitroprusside (1±1 minute), but shorter than other calcium antagonists (for example, felodipine (59±26 minutes). Clevidipine's main metabolite (H152/81) had no effect on the BP of anaesthetised SH rats when given at a molar dose 70 times higher than that required for clevidipine to lower arterial BP by 30%. Clevidipine is a racemate of R- and S-enantiomers and these were found to have the same potency and effect duration for lowering BP in anaesthetised SH rats.

Clevidipine was also tested in conscious, normotensive dogs where a dose range of 20-30 nmol/kg/min caused a blood pressure decrease of 20% with a corresponding reflex tachycardia.

Overall, the pharmacodynamic studies support the utility of clevidipine in lowering BP in a perioperative setting and demonstrate the rapidity of reversal of its antihypertensive action.

Secondary pharmacodynamics

Possible inhibition of specific ligand binding by a panel of 96 different receptors in the presence of clevidipine or its primary metabolite (H152/81) was tested at three drug concentrations (1 nM, 100 nM, and 10 μM). No receptor interactions, other than the expected inhibition of L-type calcium channel binding, were identified at or below 100 nM (expected clinical concentration). Clevidipine inhibited binding at the adenosine A_{2A} and thromboxane A_2 (TxA_2) receptors at 10 μM, which is 100 times the clinical concentration. H152/81 also showed inhibition of the thromboxane A_2 receptor (a stimulator of platelet aggregation and clot formation) at 10 μM (steady state level of H152/81 is estimated to be about 30 μM when clevidipine is infused at the maximum dose of 32 mg/hr). However, clevidipine dosing in hypertensive rats produced a modest decrease in wound bleeding time (rather than the increase that might have been expected if the inhibition at the thromboxane A_2 receptor was of physiological significance) probably due to the lowering of BP. Moreover, repeat dose studies of 28 days duration in rats and dogs failed to reveal any of the expected effects of TxA_2 antagonism (for example, prolonged bleeding) up to steady state plasma concentrations for clevidipine, ranging from 86 nM (rat) to 972 nM (dog) compared with 50-100 nM (humans); for H152/81 ranging from 216 μM (rat) to 6.8 μM (dog) compared with 10 to 30 μM in humans. Overall, the secondary pharmacodynamic studies suggest that the action of clevidipine is highly specific.

Clevidipine is intended for use in combination with anaesthetics and other drugs frequently used in association with general anaesthesia. Specific pharmacodynamic drug interaction studies were not presented by the sponsor. However, a report in the scientific literature

demonstrated that simultaneous exposure to clevidipine and isoflurane (a volatile anaesthetic that blocks neurotransmitter release by inhibiting intracellular calcium entry through both L- and other types of calcium channels) produced a small but statistically significant decrease in the concentration of isoflurane required to block nociception in the rat, and had no effect on awakening time following anaesthesia in dogs.

Safety pharmacology

GLP-standard safety pharmacology studies examined the possible effect of clevidipine dosing on the central nervous system (CNS), cardiovascular, respiratory, renal, gastrointestinal, and neuromuscular systems.

Intravenous (IV) dosing at up to 66 mg/kg/day (delivered at 200 nmol/kg/min) of clevidipine for up to 4 weeks had no effect on gross behaviour in rats (both SH and normotensive) and dogs. Clevidipine had no effect on heart rate (HR) in anaesthetised rats and dogs, however, there was a significant increase in HR (but no arrhythmias or other electrocardiographic (ECG) irregularities) in conscious rats and dogs. Repeat IV dosing of conscious, SH rats at up to 4 mg/kg (delivered at 195 nmol/kg/min) of clevidipine produced no effects on respiration as judged by blood pH, carbon dioxide partial pressure (pCO_2), oxygen partial pressure (pO_2), and base excess. Repeat IV dosing at up to 1.64 mg/kg (delivered at 90 nmol/kg/min) of clevidipine produced probable renal vasodilation as evidenced by a decrease in urine flow. Gastric emptying and intestinal propulsion in conscious, normotensive rats were both reduced by about 30% by a dose of 0.82 mg/kg (delivered at 90 nmol/kg/min and representing about 9-times a "therapeutic" dose in the rat) of clevidipine. This effect is consistent with the propensity of calcium channel blockers to cause constipation.

Skeletal muscle contractility induced by direct or efferent nerve stimulation was not affected by clevidipine at 1 nM to 10 μM. Bradycardia induced by vagal nerve stimulation and tachycardia induced by sympathetic nerve stimulation were not inhibited by clevidipine delivered at 54 nmol/kg/min to anaesthetised dogs. Both spontaneous and sympathetic nerve stimulation-induced smooth muscle contractility in the rat portal vein were inhibited with similar potency by clevidipine suggesting that the drug's action is not mediated via the neural system. None of these results indicate significant safety issues of concern.

Pharmacokinetics

Single- and repeat-dose studies

Major studies were performed using rats and dogs, and a more limited study used rabbits. These species were also used in the safety pharmacology, metabolism, toxicity, and reproduction and development studies. All studies involved IV infusion of drug and measurement of clevidipine and/or H152/81 levels in arterial blood samples using mass spectroscopy and liquid chromatography techniques, respectively. The major conclusions from these studies were:

(a) Clevidipine has linear pharmacokinetics. This is indicated by the limited sampling of steady-state blood plasma concentration (C_{SS}) data presented in Table 1.

(b) Clevidipine has a short half-life ($t_{1/2}$) in all species examined and is rapidly hydrolysed to its major metabolite H152/81 with bi-exponential kinetics. $t_{1/2}$ values under both *in vivo* and *ex vivo* conditions are shown in Table 2. A relatively slower hydrolysis rate may explain the higher C_{SS} values found in humans.

(c) Clevidipine rapidly reaches a C_{SS} level following continuous IV infusion (within 2-5 minutes in experimental species).

(d) Clevidipine has similar pharmacokinetics in both sexes.

(e) Calculated blood clearance values in rats, rabbits, and dogs were markedly higher than blood flow rates, suggesting extensive extrahepatic clearance of clevidipine.

(f) H152/81 also showed bi-exponential removal kinetics with $t_{1/2}$ values of 0.38 ± 0.13 and 0.27 ± 0.07 hours for the rapid phase and $t_{1/2}$ values of 12.8 ± 1.5 and 18.8 ± 3.1 hours for the slower phase in male and female rats, respectively. The longer half-life value for the slower phase of metabolite decline in female rats was statistically significant. Reflecting its slower rate of removal, there was approximately a thousand-fold difference between clevidipine and H152/81 levels in blood during dosing of rats. In dogs, however, the ratio was about 10.

(g) Repeat-dose studies showed an increase in clevidipine C_{SS} levels at later days, particularly at higher dosing rates. This increase appeared to be related to a decrease in the rate of clevidipine hydrolysis. In dogs dosed for 12 hours/day at 50 nmol/kg/min, the $t_{1/2}$ value of the rapid component of clevidipine hydrolysis increased from 0.73 to 1.35 minutes between days 1 and 28, respectively, and the $t_{1/2}$ value of the slower component increased from 13.1 to 16.4 minutes, respectively, over the same time period.

Table 1: Steady-state blood plasma concentrations (C_{SS}) of clevidipine on day 1 of infusion

Species	Dose rate (nmol/kg/min)	C_{SS} (nM)
Rat	20	59
	67	223
	200	556
Rabbit	54	156
	83	281
Dog	50	149
	100	257
	300	697
Human	0.7 - 7	10 – 100

Table 2: Clevidipine hydrolysis kinetics: $t_{1/2}$ values in blood at 37°C

Species	*In vivo*		*Ex vivo*
	Rapid phase	**Slow phase**	
Rat	16-19 secs (80%)[a]	ND	34 ± 5 secs
Rabbit	13 secs (95%)	3.2 mins	ND
Dog	40-45 secs (80-85%)	13.1 mins	15.7 ± 3.2 mins
Human	~ 1 min (85-90%)	~ 15 mins	5.8 ± 1.1 mins

Abbreviation: ND = not determined; [a] Fraction of drug cleared by this phase.

Protein binding

Clevidipine (and its two enantiomeric forms) showed >99% binding to blood plasma protein from rats, rabbits, dogs, pigs, and humans. Percent binding to human blood plasma protein was constant over the range 25 to 250 nM clevidipine.

Tissue distribution

The volume of distribution from pharmacokinetic (PK) studies (0.45L at steady state in the rat, 0.17L/kg in rabbit and 2L/kg in dog) was suggested by the sponsor to reflect limited distribution. However, radiolabel distribution studies (particularly ^{14}C) suggested rapid and widespread distribution of drug associated radioactivity. Tissue distribution studies used ^{3}H- or ^{14}C-labelled clevidipine given to rats as a single IV infusion. The ^{3}H atom was attached to the phenyl group of clevidipine, however, the ^{14}C label was in a sidechain and is released as formaldehyde (capable of reacting with a range of cellular molecules) during *in vivo* metabolism of clevidipine. By 1-5 minutes after dosing with the^{3}H-labelled compound, there were high to very high radioactivity levels in blood, myocardium, lung, pigmented layer of the eye, choroid plexus, adrenal medulla and cortex, diaphragm, tongue, dental pulp, and brown fat. By 4-16 hours post-dosing, ^{3}H levels in most of these tissues were declining. Very high ^{3}H levels were present in urine and intestinal contents by 1 and 4-16 h post-dosing, respectively, and there were high levels in bile by 15 minutes. Radioactivity was not detected in any tissue/organ by 8 days after dosing. In the pregnant rat, only low levels of ^{3}H were seen in fetuses at all time points. The results from rats infused with [^{14}C]-clevidipine presented a somewhat different picture. ^{14}C levels in 25 of 64 measured tissues/fluids had reached a maximum by 1 hour after dosing. Most tissues showed higher ^{14}C levels than blood. Tissue systems showing the highest ^{14}C levels were vascular (bone marrow and spleen), excretory (kidney, liver, bladder, urine), endocrine (adrenal, pituitary, thymus, thyroid) and secretory (pancreas, salivary gland). Testes showed low levels of radioactivity. ^{14}C levels in most tissues started to decline during 24-72 hours post-dosing. Significantly greater ^{14}C levels were associated with melanin-containing tissues in eye and skin in pigmented versus albino rats. It was estimated that 2.4% of total input ^{14}C remained in tissues at 72 hours post-dose in albino rats, and 0.4% at 28 days in pigmented rats.

Metabolism and excretion

Clevidipine is converted by ester hydrolysis of its major sidechain to its primary inactive metabolite M1 (H152/81). The latter compound can be oxidised to produce the corresponding pyridine M2. Alternatively, M1 can undergo acyl-glucuronidation to produce M3, or it can be decarboxylated to produce M4 and the corresponding oxidation product M5. The central role of ester hydrolysis in clevidipine metabolism was supported by the finding of slower reaction kinetics, under *ex vivo* conditions, in blood from homozygous pseudocholinesterase-deficient versus control humans ($t_{1/2}$ values of 9.3 ± 1.7 and 5.8 ± 1.1 minutes, respectively). By around 1.5 hours after clevidipine dosing, M1 (H152/81) was the only metabolite detectable in human blood. Formaldehyde can be expected to be generated (in a 1:1 ratio to parent) as a metabolite of clevidipine by esterases present *in vivo* or *in vitro (*for example, S9 mixes in genotoxicity assays). The safety implications of this are discussed in detail in the *Genotoxicity* section below.

The major route of clevidipine metabolite excretion in rats and dogs was via faeces (~ 55-70% elimination by this route), suggesting biliary elimination. The M5 oxidation product was the major metabolite present in faeces from rats, dogs, and humans. Little or no excretion of unmodified clevidipine was found in all three species examined. In humans, urine was the major route for excretion of clevidipine metabolites and accounted for around 68% of the initial dose as compared with around 15% for faeces. The acyl-glucuronidation product M3 was the major metabolite present in human urine. For both rats and dogs, excretion predominantly occurred within 72 hours of dosing. In humans, 83% of a dose of [^{3}H]-clevidipine had been excreted in faeces or urine by 7 days post-dosing.

Data from the exposure of human hepatocytes and human cytochrome P450 (CYP) enzymes to clevidipine or its major metabolite H152/81 indicated only minor responses. One exception

was CYP3A4 which showed an approximate 10-fold induction after exposure of hepatocytes to high concentrations (100 μM) of clevidipine or H152/81. However, such high concentrations are unlikely to be clinically relevant and therefore therapeutic doses of clevidipine are unlikely to significantly induce CYP activity and are unlikely to inhibit drug metabolism via CYP activity.

Pharmacokinetic drug interactions

The effect of several drugs that are commonly used in association with general anaesthesia on the hydrolysis of clevidipine in human blood was determined. Thiopental sodium (to 1500 μg/mL), fentanyl (to 200 ng/mL), morphine (to 5000 ng/mL), diltiazem (to 10 μg/mL), propofol (to 250 μg/mL), and isoflurane (to 3000 μg/mL) all had no significant effect on the rate of clevidipine hydrolysis. Two neuromuscular blocking drugs, pancuronium bromide and vecuronium bromide, produced a moderate (~25%) decrease in the rate of clevidipine hydrolysis. The clinical significance of this finding, if any, is unclear.

Relative exposure

Clevidipine steady-state concentrations in blood plasma were multiplied by the daily dosing time (either 12 or 24 hours) to give an area under the concentration time curve (AUC) value. Because steady-state concentration values generally increased during the dosing period (up to 28 days), an average of values obtained during the dosing period was used in this calculation. An exposure ratio was derived by dividing the animal AUC values by an AUC value from healthy humans given the maximum recommended clevidipine dose rate (32 mg/hr) (Table 3). The exposure ratio values indicate that the highest dose rates used in rat repeat-dose toxicology studies gave AUC values comparable to those at the maximum anticipated clinical dose in humans, and those used in dog studies were up to 3-4 times human values.

Table 3: Relative exposure to clevidipine during repeat-dose studies

Study type	Species & strain	Treatment duration/ hours/day	Dose rate (nmol/kg/ min)	C_{SS} (nM)[a]	AUC[b]	Exposure ratio[c]
repeat-dose tox.	Rat (SD)	7 days/ 12 h	10	17.8	214	0.1
			35	47.1	565	0.2
			100	171	2050	0.9
repeat-dose tox.	Rat (SD)	14 days/ 12 h	10	29.6	355	0.1
			35	68.5	821	0.3
			100	244	2928	1.2
repeat-dose tox.	Rat (SD)	28 days/ 12 h	10	21.2	255	0.1
			35	57.8	694	0.3
			100	189	2268	0.9
repeat-dose tox.	Rat (SD)	28 days/ 24 h	35	22.4	538	0.2
			60	40.8	979	0.4
			100	67.4	1616	0.7
repeat-dose tox.	Dog (beagle)	5 days/ 12 h	25	162	1938	0.8
			50	280	3360	1.4
			150	805	9654	4.0

repeat-dose tox.	Dog (beagle)	28 days/ 12 h	10	56.5	678	0.3
			25	160	1919	0.8
			50	256	3072	1.3
			100	651	7812	3.3
SAD-0001	Human (normal subjects)	24 hours	14.7	99.7	2392	1

[a]C_{SS} is clevidipine steady-state concentration. The figure shown is the average of values obtained at different days during the dosing period: days 1 and 7 (report no. T2969); days 1 and 14 (report no. T3054); days 1, 7, and 28 (report nos. T2968 and T2967); days 7 and 28 (report no.96008); and days 1 and 5 (report no. T2956); [b]AUC is C_{SS} multiplied by dosing time per day (i.e. 12 or 24 hours); [c]Ratio of animal to human AUC values.

Toxicology

As previously mentioned in the *Introduction*, findings from many of the toxicology studies were difficult to interpret due to vehicle effects (Intralipid) and/or poor animal husbandry. Single and repeat dose toxicity are briefly discussed below but the main nonclinical issues related to genotoxicity and reproductive effects of clevidipine.

Single-dose toxicity

The acute toxicity of IV administered clevidipine was examined in both sexes of rats and mice. The mouse studies suggested a maximum non-lethal dose of 310 μmol/kg (140 mg/kg) and a minimum lethal dose of 380 μmol/kg (180 mg/kg). Ataxia, respiratory difficulties, cyanosis, and convulsions were observed soon after dosing. Deaths usually occurred immediately or shortly after dosing. Rats showed irregular breathing and decreased motor activity shortly after clevidipine dosing and for up to 45 minutes later. Death usually occurred minutes after dosing and was preceded by dyspnoea, cyanosis, and in some cases convulsions. The maximum non-lethal dose in male rats was 240 μmol/kg (110 mg/kg) and deaths occurred at 280 μmol/kg (130 mg/kg). Female rats were more sensitive to clevidipine and death occurred at 200 μmol/kg (91 mg/kg).

Repeat-dose toxicity

IV dosing, for 12 or 24 hours per day, was conducted in rats and dogs for up to 4 weeks. The key studies were performed by established pharmacology laboratories according to GLP procedures, and used both sexes and standard testing times and group numbers.

Rats that were continuously IV dosed at up to 100 nmol/kg/min of clevidipine for up to 4 weeks, showed no drug-related mortality and no obvious drug-related clinical signs. Changes that were seen in experimental rats (such as decreased food consumption and increases in some organ weights) were considered solely/largely attributable to vehicle- or surgery-induced effects (i.e. changes were seen in both drug-treated and vehicle-control groups or change lacked dose dependency). The pivotal rat 4-week study suggested a NOAEL of 39 mg/kg/day (exposure ratio of about 0.4).

Dog studies generally revealed similar outcomes to those found with rodents. Changes seen after dosing were minor and were considered solely/largely attributable to the vehicle. Dose-dependent decreases in absolute and relative testis weight were observed in both a preliminary 4 week IV study and in a follow-up 2-week dosing study. In the latter study, animals dosed at 66 mg/kg/day (12h/day; corresponding to a relative exposure of about 3 based on AUC)) showed a statistically significant decrease in testis weight that was reversible during a 4-week recovery period. The study pathologist proposed that there were no effects

on male reproductive parameters such as sperm motility, sperm count, and sperm morphology other than those usually associated with an immature dog but conceded that interpretation of the pathology findings was confounded by high individual variability. In the absence of any hypo/aspermatogenesis being observed any of the saline or lipid control groups, the pathologist's suggestion that this is purely a background lesion in immature dogs (6% incidence in beagles aged 2.5 to 7.5 years old; Rehm, 2000) is not compelling.[4] This raises the possibility that clevidipine may interfere with spermatogenesis in line with other calcium channel blockers. However, there were no effects of clevidipine on testicular weight, sperm parameters or male fertility in rats in the repeat dose and/or or reproductive toxicity studies at doses up to 66 mg/kg/day.

One of four dogs in the 2 week study also showed slight myocardial degeneration/necrosis of the papillary muscle and left ventricle, consistent with lesions observed with high doses of other antihypertensive agents. A NOAEL of about 16 mg/kg/day was suggested for the latter study (clevidipine C_{SS} values were not available) which, based on the results shown in Table 3, corresponds to an exposure similar to that anticipated clinically.

Genotoxicity

A positive result was obtained in the Ames assay when bacteria, clevidipine, and S9 metabolic activation mixture were pre-incubated at 37°C for 30 minutes prior to growth on agar plates. It was suggested by the sponsor that mutation induction is attributable to formaldehyde produced during clevidipine metabolism. No direct evidence in support of the latter claim was presented. The sponsor's research did show, however, that: (1) formaldehyde is a mutagen in the Ames assay and its mutagenicity is decreased by addition of formaldehyde dehydrogenase (FDH); and (2) inclusion of bacterial FDH in the pre-incubation mixture significantly reduced the number of revertants induced by clevidipine. Nevertheless, the results provided suggested that bacterial FDH was less effective in protecting against clevidipine- than formaldehyde-induced mutagenesis. Possible explanations include: a) clevidipine induces mutations both via formaldehyde and via other metabolite(s) that are not removed by FDH, b) metabolism of clevidipine produces a mutagen that is less effectively removed than formaldehyde by FDH, c) insufficient FDH was added to maintain clevidipine-generated formaldehyde below a mutagenic threshold (for example, it was sufficient to block 15-30µg/plate of added formaldehyde but not up to 300-900µg/plate clevidipine depending upon the strain).

Mutagenesis by clevidipine was also demonstrated using a mammalian cell line. A dose-dependent induction of homozygous-deficient mutants at the thymidine kinase locus of mouse lymphoma L5178Y $TK^{+/-}$ cells was shown when cells were incubated with clevidipine at 37°C either with or without addition of S9 mixture for 4 hours and then plated in selective medium. Addition of S9 mixture did, however, significantly increase mutant yield. In these experiments, addition of FDH to the cellular incubation mixture reduced mutation yield to near-background levels.

Clastogenicity was tested using *in vitro* cultured human peripheral blood lymphocytes and showed that clevidipine induced a dose-dependent increase in the frequency of chromosomal aberrations. This effect was markedly increased by addition of S9 mix and reduced, to near-background levels, by addition of FDH. A second study, also using *in vitro* cultured human peripheral blood lymphocytes, likewise demonstrated a dose-dependent increase in the

[4] Rehm, S. Spontaneous testicular lesions in purpose-bred beagle dogs. *Toxicological Pathology* 2000; **28:** 782-87.

frequency of chromosomal aberrations after clevidipine exposure. In this study, however, the yield of chromosomal aberrations was less markedly increased by addition of S9 mix and there was still a significant yield of chromosomal aberrations when cells were incubated in the presence of bacterial FDH.

In the only *in vivo* clastogenicity assay, there was no significant increase in the frequency of micronucleated erythrocytes in mice that had been given a single IV infusion of clevidipine. With respect to this result a senior FDA reviewer noted (NDA 22-156):

I interpret the negative findings to the high-reactivity of formaldehyde with proteins - which denies it access to erythroblast chromosomes -rather than to the assay being insensitive or inappropriate for testing clastogenicity of formaldehyde pro-drugs. Accordingly, I am re-assured by the negative findings in this assay, and would be even more so if the mouse erythroblast were tested in vitro, and shown to be vulnerable to clevidipine plus S-9 metabolic enzymes. Certainly the mouse lymphoma cell was susceptible in vitro to the genotoxicity of clevidipine + S9, the latter combination, in fact, equalling the toxicity of the positive control.

Although it is reassuring that short-term clevidipine exposure in mice did not significantly increase the frequency of micronuclei in erythrocytes, the ability to extrapolate this result to other cell types that might be exposed to clevidipine or its metabolites was not explored. Furthermore, there was no investigation by the sponsor of possible mutagenicity in an alternative *in vivo* system such as a transgenic mouse model.

Overall, the following weight of evidence suggests that clevidipine does not represent a genotoxic risk in humans at the proposed clinical doses and exposures:

- FDH largely reversed the positive findings seen in the presence of S9 *in vitro*.
- In contrast to the genotoxicity of clevidipine, felodipine (which is structurally very similar but does not generate formaldehyde as a metabolite) was neither mutagenic nor clastogenic in the same panel of tests.[5]
- Quantitative estimates of the steady state plasma concentration of formaldehyde generated in a 1:1 ratio by clevidipine are about 200 to 400 nM. This is 400-600 times less than the endogenous level of 67-100 µM reported in the literature (Heck & Casanova, 2004).[6] Therefore, the extra formaldehyde load imposed by clevidipine metabolism is insignificant in the face of normal endogenous formaldehyde generation.
- The formaldehyde generated *in vivo* per dose of other prodrugs (fosphenytoin, fospropofol, cefditoren, adefovir dipivoxil) is in the range of 1 to 103 mg, and includes that afforded by clevidipine (50 mg/day).
- The amount of formaldehyde generated by clevidipine is much less than the amounts needed to induce excess sister chromatid exchange in human blood *ex vivo* (> 100 µM) and did not induce excess micronuclei even up to 250 µM (Schmid & Speit, 2007).[7] As Comet assays have shown that formaldehyde can induce DNA-protein cross-links at ≥ 25µM it appears that cross-links must be removed enzymatically or

[5] http://www.fda.gov/medWatch/SAFETY/2003/03Jun_PI/Lexxel_PI.pdf

[6] Heck H, Casanova M. The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. *Regulatory Toxicology & Pharmacology* 2004; **40**: 92-106.

[7] Schmid O, Speit G. Genotoxic effects induced by formaldehyde in human blood and implications for the interpretation of biomonitoring studies, *Mutagenesis* 2007; **22**: 69-74.

otherwise before the lymphocytes start to replicate, thus preventing irreversible gene damage.

Carcinogenicity

No carcinogenicity studies were performed for clevidipine as it is only proposed for short term use. Lifetime carcinogenicity studies with other calcium channel blockers (CCB) such as nifedipine, nimodipine, nisoldipine and nitrendipine have not yielded evidence for a carcinogenic potential of these compounds. Moreover, the mechanistic knowledge on the influence of CCB on the fundamental processes of cell proliferation and apoptosis is not in favour of a tumour-promoting activity of these compounds (Ahr *et al*., 1998).[8]

Clevidipine metabolism yields the genotoxic metabolite, formaldehyde, which is listed by the US Environmental Protection Agency (EPA) as a probable human carcinogen and by the American Conference of Governmental Industrial Hygienists (ACGIH) as a suspected human carcinogen. However, given the short term use and the insignificant quantitative generation of formaldehyde compared with normal endogenous production (see discussion below), the carcinogenic risk of clevidipine in an acute setting is considered minimal.

Reproductive and developmental toxicity

All reproductive and developmental stages (that is, fertility and early embryonic development, embryo-fetal development, pre- and postnatal development) were examined for possible effects of clevidipine dosing. The species examined (rat and rabbit), the number of animals per group, the timing and duration of treatment, and the drug doses used, were appropriate. These studies conformed to GLP standards.

Only two of the reproductive and developmental toxicity studies included measurements of blood plasma levels of clevidipine or its metabolite H152/81. A study of male rat fertility used animals that had been continuously IV dosed with clevidipine for 28 days as part of a repeat-dose toxicity study. Exposure values, relative to the maximum recommended human dose, for the latter rats ranged from 0.2 to 0.7 (Table 3). Two other rat reproductive and developmental toxicity studies used dose rates within the range of the latter study and thus presumably covered a similar range of exposure ratios. The rat embryo-fetal development toxicity study measured blood plasma levels of H152/81 in dams. These values have been compared to H152/81 concentrations measured in blood plasma from humans dosed at 16 mg/day with clevidipine (Table 4). The calculated exposure ratios are markedly higher than those derived from clevidipine measurements (Table 3), despite the fact that all studies covered a similar range of clevidipine infusion rates. The explanation for this difference is unclear but might, for example, reflect inter-species differences in the relative rates of removal of clevidipine and H152/81 from blood plasma.

Drug blood plasma concentrations were not measured in the rabbit embryo-fetal development study. A PK study, which used a different strain of rabbit, estimated blood plasma C_{SS} values of 156 and 281 nM when clevidipine was dosed at rates of 54 and 83 nmol/kg/min, respectively. The latter figures were used to derive estimates for C_{SS} in the embryo-fetal development study, leading to relative exposure values (as compared with the AUC value for humans given the maximum recommended clevidipine dose) of 1.6 to 3.1.

[8] Ahr HJ, Bomhard E, Enzmann H et al. Calcium channel blockers and the risk of cancer: a preclinical assessment, *Cardiovascular Drugs & Therapy* 1998; **12**:157-69.

Table 4: Relative exposure to H152/81

Report no. (study type)	Species & strain	Treatment duration/ hours per day	Dose rate (nmol/kg/ min)	C_{SS} (μM)[a]	AUC[b] (μM*24h)	Exposure ratio[c]
97003 (embryo-fetal toxicity)	Rat (SD)	11 days (day 6 to 17 *post coitum*)/ 24 h	20	83.0	1992	4.0
			53	130	3120	6.2
			84	178	4272	8.5
SAD-0018	Human normal subjects)	24 hours	7.0	10.4	250	-

[a]C_{SS} is H152/81 steady-state concentration. The figure shown for the rat study is the median of two determinations on day 16 *post coitum*; [b]AUC is C_{SS} multiplied by dosing time per day (i.e. 24 hours); [c]Ratio of rat to human AUC values (human AUC value was from individuals dosed at 16 mg/day, accordingly value was multiplied by 2 to be equivalent to exposure from the maximum recommended dose).

No effects on mating performance, fertility, or early embryonic development were noted when male rats were IV dosed with clevidipine at up to 55 mg/kg/day for 28 days prior to mating. Unlike the dog studies, detailed male reproductive assessments of rats showed no effects on weights of reproductive organs, sperm motility, sperm morphology, sperm count, or testicular histopathology. Exposure to clevidipine at the NOAEL of 55 mg/kg/day is likely to be similar to human exposure at the Maximum Recommended Human Dose (MRHD) (based on either AUC or Body-Surface Area (BSA) adjusted daily dosage).

While there were no effects of clevidipine (at up to 55 mg/kg/day) on female fertility in rats dosed from 14 days prior to mating until 7 days *post coitum*, some treated animals showed oestrous cycles of unusual duration (longer or shorter than normal) or were pseudopregnant, prior to mating. These effects have not appeared with other calcium channel blockers and were not dose related. In the absence of any mechanistic data it can only be speculated that clevidipine has an endocrinological effect in rats, which does not impair fertility.

An embryo-fetal development toxicity study indicated significant maternal and possible embryo-fetal toxicity when mated rats were continuously IV infused with clevidipine from days 6 to 16 *post coitum* at 100 nmol/kg/minute. A similar study in which mated rats were continuously IV infused from days 6 to 17 *post coitum* at dose rates up to 84 nmol/kg/minute indicated that clevidipine dosing had a slight retarding effect on fetal development but that there were no skeletal or soft-tissue effects indicative of teratogenic potential. A NOAEL of 13 mg/kg/day (20 nmol/kg/min) was suggested, corresponding to about one-fifth of the anticipated exposure to clevidipine at the MRHD (based on BSA) or 4X the anticipated clinical exposure to H152/81 at the MRHD.

As noted above (*Tissue distribution*), only low levels of clevidipine or its metabolites were found in the fetuses of dosed, pregnant rats. Dutch rabbits showed poor tolerance of the vehicle used for infusions. Accordingly, a major embryo-fetal toxicity study employed New Zealand white (NZW) rabbits, which showed better vehicle tolerance. In this study, pregnant rabbits were continuously IV infused at dose rates up to 84 nmol/kg/minute from day 7 to 19 of gestation. There was no evidence of teratogenicity at any dose rate or of effects on numbers of corpora lutea, implantation sites, live fetuses, dead fetuses, or sex ratio. However, the primary observation at the high dose was an increased abortion rate preceded by periods of poor food consumption. A NOAEL for rabbit embryo-fetal development of 35 mg/kg/day

(53 nmol/kg/min) was suggested, corresponding to a relative exposure margin at the MRHD of about 2 to 3 (based on AUC).

In pregnant rats dosed with clevidipine butyrate during late gestation and lactation, there were dose-related increases in maternal mortality, length of gestation and prolonged parturition at doses greater than or equal to 13 mg/kg/day (1/6 of the MRHD based on BSA). No NOAEL was established. All rats dosed at 35 mg/kg/day and most rats dosed at 55 mg/kg/day died. Death (or unscheduled euthanasia) was associated with birthing difficulties. Other calcium channel blockers have been shown to prolong parturition and increase the incidence of perinatal death in rats due to inhibition of uterine contractions.

Evaluation of the F1 generation was somewhat compromised by poor survival, with F1 viability showing a dose-related decrease and an effect from the lipid vehicle. There were slight decreases in the time for F1 drug-treated pups to reach the day of tooth eruption and eye opening. F1 females showed a slight increase to the time of vaginal opening. The significance, if any, of these observations is unclear. Fertility of the F1 generation was apparently decreased in those pups who had received early exposure to clevidipine.

Overall, the reproductive toxicology of clevidipine was consistent with other drugs in its class. However, clevidipine does appear to be unique in inducing atypical oestrous cycle length and pseudopregnancy in rats, the significance of which is unclear.

Paediatric use

Studies that specifically examined the effects of clevidipine in young animals were not performed. Clevidipine is not currently recommended for use in children or adolescents.

Phototoxicity and local tolerance

Possible phototoxic potential of clevidipine was not specifically examined, however, based on its relatively rapid metabolism, lack of long-term tissue accumulation, and lack of irritation in skin and blood vessel tests, such activity would seem unlikely.

Nonclinical Summary and Conclusions

The critical studies examining repeat-dose toxicity, genotoxicity, and teratogenicity were apparently performed according to GLP standards but interpretation of many of the general toxicology studies was confounded by use of Intralipid as a vehicle and/or poor animal husbandry procedures.

Pharmacodynamic studies showed that clevidipine butyrate is a highly lipophilic, dihydropyridine class antihypertensive that has the following properties: 5-fold less potent than felodipine in vitro; high vascular:myocardial selectivity ratio (>50); hypotensive potency in anaesthetized SH rats > conscious SH rats > normotensive rats; rapid loss of hypotensive activity; main metabolite (H152/81) has 70-fold lower potency than parent; R- and S-enantiomers of the racemate have equal activity; selective for dihydropyridine receptors at clinical concentrations with some binding to thromboxane A2 receptors at 100-fold clinical concentrations.

Safety pharmacology studies covering the CNS, cardiovascular, respiratory, renal, gastrointestinal, and neuromuscular systems showed a lack of significant detrimental effects.

Pharmacokinetic studies in rats, rabbits and dogs that were IV infused with clevidipine showed: linear pharmacokinetics; similar pharmacokinetics in both sexes; rapid hydrolysis in blood with bi-exponential kinetics ($t_{1/2}$ value of major removal phase ranged from 16-19 s in rats to about 1 min. in humans); rapid attainment of a steady-state concentration (within 2-5 minutes in animal models); and extensive extra-hepatic clearance. Greater than 99% of

clevidipine was bound to blood plasma protein in humans and all tested nonclinical species. The volume of distribution from PK studies (0.45L at steady state in the rat, 0.17L/kg in rabbit and 2L/kg in dog) was suggested by the sponsor to reflect limited distribution. However, radiolabel distribution studies (^{14}C; associated with the hydrolysable sidechain) also suggested a component of rapid and widespread distribution of drug associated radioactivity, probably reflecting eventual formaldehyde formation and incorporation into the one-carbon cellular metabolic pool.

In blood, clevidipine is rapidly converted by ester hydrolysis of its major sidechain to its primary inactive metabolite (H152/81). The latter compound can undergo oxidation, decarboxylation, and acyl-glucuronidation reactions. The major route of excretion was via faeces in rats and dogs and via urine in humans. In both rats and dogs, clevidipine excretion occurred predominantly within 72 hours of dosing.

Cytochrome P450 isoforms appeared insensitive to inhibition by clevidipine or H152/81 and only CYP3A4 showed a modest induction in drug-exposed hepatocytes. It was concluded that clevidipine dosing of patients is unlikely to induce CYP activity or inhibit drug metabolism via affects on CYP activity.

Repeat-dose toxicity studies were conducted in rats (up to 4 weeks) and dogs (up to 4 weeks). Exposure ratios, based on relative blood plasma clevidipine levels, were comparable in rats and around 3-4 times greater in dogs than recommended maximal dosing for humans. Most changes seen in experimental animals during dosing were largely attributable to vehicle- or surgery-induced effects. While decreased testis weight and possible hypo-aspermatogenic changes were observed in dogs at low exposures no such changes were observed in rats at similar exposures.

Clevidipine displayed positive genotoxic potential in *in vitro* assays (Ames test, mouse lymphoma thymidine kinase locus assay, chromosomal aberration assay) but not *in vivo* in the mouse micronucleus test. The positive *in vitro* results were consistent with the formation of formaldehyde, a likely metabolite of clevidipine, which is known to be genotoxic *in vitro* and a probable human carcinogen. However, human *in vivo* exposure to formaldehyde at the maximum clinical dose of clevidipine (32 mg/h) was at least several hundred times less than normal daily endogenous formaldehyde generation. Furthermore, there is extensive postmarket clinical experience with other prodrugs that are known to generate formaldehyde in a similar range. Genotoxicity observed *in vitro* is, therefore, not of clinical concern.

Long-term studies for the evaluation of carcinogenicity were not performed with clevidipine due to the intended short-term duration of human use.

Clevidipine dosing did not cause significant effects on mating performance, fertility, or early embryonic development in rats at exposure levels similar to that anticipated clinically at the maximum recommended human dose (MRHD). Embryofetal development studies in rats showed a slight retarding effect on fetal development but no skeletal or soft-tissue effects indicative of teratogenic potential. There was decreased fetal survival when pregnant rats and rabbits were treated with clevidipine butyrate during organogenesis at doses 0.7 times (on a body surface area basis) the MRHD in rats and 2 times the MRHD in rabbits. In pregnant rats dosed with clevidipine butyrate during late gestation and lactation, there were dose-related increases in maternal mortality, length of gestation and prolonged parturition at doses greater than or equal to 1/6 of the MRHD based on body surface area, probably reflecting drug-induced inhibition of uterine contractions, a class effect of calcium channel blockers.

Pharmacodynamic studies supported the utility of clevidipine in lowering BP in a perioperative setting and demonstrated the rapidity of reversal of its antihypertensive action.

The major toxicity issue concerned the positive genotoxicity findings observed with clevidipine *in vitro*, which were consistent with the metabolic formation of formaldehyde, which is known to be genotoxic *in vitro* and a probable human carcinogen. However, human *in vivo* exposure to formaldehyde at the maximum clinical dose of clevidipine (32 mg/h) was estimated to be at least several hundred times less than normal daily endogenous formaldehyde generation in the one carbon cellular metabolic pool. Furthermore, there is extensive postmarket clinical experience with other prodrugs that are known to generate formaldehyde in a similar range (fosphenytoin, fospropofol, cefditoren, adefovir dipivoxil). Therefore, there is no cause for clinical concern.

The reproductive toxicity of clevidipine was largely consistent with class effects of calcium channel blockers (Category C) and can be suitably addressed in the PI.

The critical studies examining repeat-dose toxicity, genotoxicity, and teratogenicity were performed according to GLP standards. Nevertheless, the TGA evaluator agreed with the FDA assessment (NDA 22-156) that the interpretation of the general toxicology of clevidipine was impeded by the use of Intralipid as a vehicle: the vehicle alone caused body weight, clinical chemistry and histopathological changes in line with its lipid nature. In some cases Intralipid also increased the apparent treatment-related effects of clevidipine. Moreover, several toxicology studies were either partially or fully compromised by poor animal husbandry whereby sepsis, keratitis, catheter closures and overall poor survival were observed.

IV. Clinical Findings

Introduction

The clinical development program includes 19 clinical studies, over 2300 subjects overall and 1406 clevidipine-treated subjects**.** Four Phase I, nine Phase II, and six Phase III studies have been completed to date. The data from the Phase II studies were not integrated and were presented as individual study data. The Phase III studies were integrated and included data from more than 1,800 patients (of which 992 received clevidipine) recruited into 6 pivotal studies. Five of these studies were conducted in patients with perioperative hypertension [ESCAPE-1 (TMC-CLV-03-01), ESCAPE-2 (TMC-CLV-03-02), ECLIPSE-NTG (TMC-CLV-03- 03), ECLIPSE-SNP (TMC-CLV-03-04) and ECLIPSE-NIC (TMCCLV- 03-05)] and 1 study was in patients with severe hypertension [VELOCITY (TMC-CLV-06-02)].

These studies were all performed in compliance with Good Clinical Practice. Clevidipine was developed up to the end of Phase II by AstraZeneca, and all AstraZeneca legacy studies are prefixed by SAD-XXXX. All studies conducted by the current sponsor, The Medicines Company, are prefixed by TMC-CLV-XX-XX. However, this submission has been lodged by Kendle Pty Limited. Results of all studies were clearly presented.

Pharmacodynamics

Pharmacodynamic (PD) data of clevidipine in healthy volunteers were derived from 4 clinical trials in which 104 volunteers participated. Three Phase I studies **(SAD-0001, SAD-0002 and SAD-0018)** in 47 healthy volunteers provide PK/PD and safety/tolerability data. An additional Phase I study **(TMC-CLV-05-01)** in 54 healthy volunteers explored the electrocardiographic safety of clevidipine. The doses of clevidipine administered in these studies ranged from 0.5 to 21.6µg/kg/min (2.4 to 103.7 mg/h for 80 kg subject) and the length of infusions ranged from 20 minutes (min) to 24 hours (h).

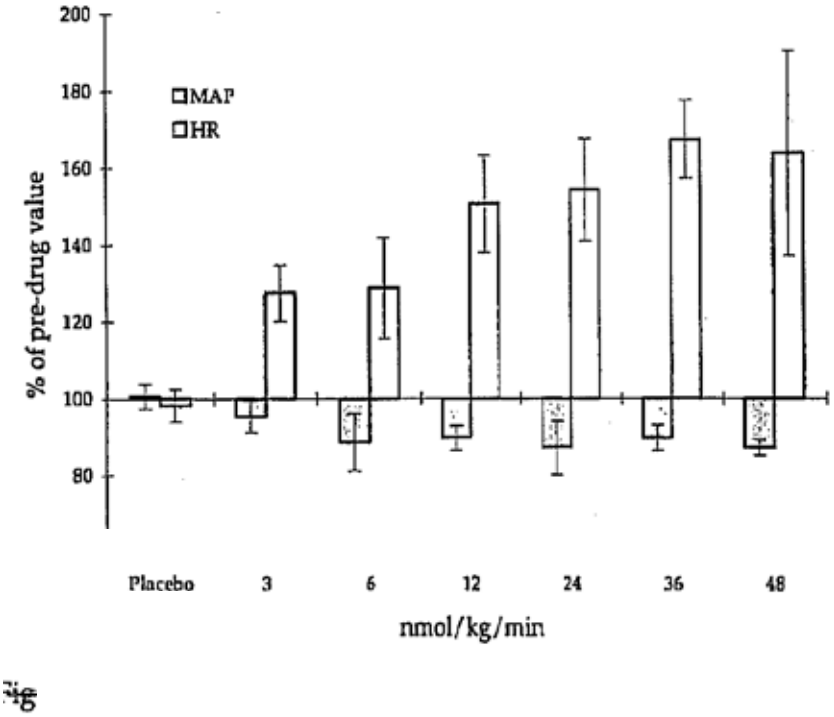
Pharmacodynamics in healthy volunteers

Phase I, PK/PD studies in healthy volunteers

In study **SAD-0018**, the time to onset of haemodynamic effect (changes in mean arterial pressure [MAP] and heart rate [HR]) was determined in 14 healthy male volunteers during a 20 minute constant infusion of clevidipine at 3.2µg/ min/kg (16 mg/h). The onset of effect was rapid and the time required establishing steady-state concentration and effect following an initial infusion or a change in administration rate was only 2 to 3 minutes. Overall, the time to onset of effect was less than 5 minutes between the start of clevidipine infusion and the attainment of maximal effect on haemodynamic parameters. There was a close correlation between the changes in ratio MAP/HR and the arterial blood concentrations with a short delay (1.1 min) between the concentrations and effect during and after the short infusion. The maximal reduction in MAP/HR (Emax) was 42% and the arterial blood concentration producing 50% of maximal effect (EC50) was 40 nmol/L**.** The time courses of the arterial blood concentrations were in close agreement with the onset of responses, with a very short time delay between the maximal arterial blood concentrations and the maximal responses and rapid reversal of pharmacodynamic changes following end of the 20-minute clevidipine IV infusion**.**

In study **SAD-0001**, after short-term (20 minutes) IV infusions of gradually increasing IV doses to 23 healthy subjects, there was no relationship found between the blood concentration of clevidipine and changes in diastolic blood pressure (DBP), MAP or HR. The reason for this is probably the pronounced baroreflex activation of the heart when arterial blood pressure is reduced by means of peripheral vasodilatation. The ratio MAP/HR was calculated as an indirect measure of peripheral vascular resistance. Figure 1 shows the relationship between the change in MAP/HR for pre-drug value and blood concentration of H 324/38. Values were obtained at dose rates 3-48 nmol/kg/min during the last 10 minutes of infusion and 5 minutes after stopping infusion. According to these results, the maximum reduction in MAP/HR (Emax) was 48.2 %, and the concentration at a half-maximum effect (EC_{50}) was 21.7 nmol/ln (this was achieved at a dose rate of approximately 3nmol/kg/min)

Figure 1: MAP and HR – steady state value (mean of 10, 15 and 20 minutes), % of pre-drug value, mean and SD, n(placebo) = 10, n(3) = 4, n(6) = 4, n(12) = 4, n(24) = 3, n(36) = 4, n(48) = 3.



Study SAD-0002 mainly looked at distribution, metabolism and excretion following administration of radiolabelled clevidipine.

Effect of therapeutic and supratherapeutic concentrations of clevidipine on ECG

The main objective of study **TMV-CLC-05-01** was to assess the safety of clevidipine in terms of its effect on cardiac repolarisation (measured by the ECG) at therapeutic (3.2 µg/kg/min or 16 mg/h) and supratherapeutic (12 µg/kg/min or 57.6 mg/h) concentrations following intravenous infusion for 22.25 hours. Continuous infusion of 3.2 µg/kg/min (16 mg/h) for 22.25 hours was intended to represent the dose at which a majority of patients demonstrate therapeutic response clinically. The supratherapeutic dose, upward titration to a maximally tolerated dose up to 12 µg/kg/min (57.6 mg/h) which was then continued for at least 20 minutes, was intended to achieve blood concentrations of clevidipine and its primary metabolite, H152/81, which are higher than those likely to be encountered clinically. The study was conducted in two phases: a pilot study (Stage I) and the Main Study. Stage I was an open-label, nonrandomised pilot study to assess the effect of Intralipid (20% IV fat emulsion) on ECG parameters; the practicality of fenoldopam[*] infusion at two rates to attain predetermined HR; and the ability to detect the effect of oral moxifloxacin on uncorrected QT during HR control infusion. The Main Study was a randomised, single-blind, vehicle (Intralipid) and HR-controlled, two-treatment crossover trial in healthy volunteers, with an additional nonrandomised, open-label positive control treatment (moxifloxacin) with HR control. HR control was fenoldopam infusion administered to achieve HR in the range expected during up-titration and supratherapeutic infusion of clevidipine. All volunteers were randomised to one of two treatment sequences for the IV infusion treatments:

[*] *Fenoldopam infusion was administered to achieve HR in the range expected during up-titration and supratherapeutic infusion of clevidipine.*

1) Clevidipine IV infusion with accompanying plain normal saline infusion simulating fenoldopam infusions during the up-titration phase; and
2) vehicle and HR-control IV infusion (Intralipid equal to the volume for that subject's clevidipine dose levels along with fenoldopam IV infusion in carefully titrated infusions during the up-titration phase).

These were followed by a third treatment phase consisting of fenoldopam with oral moxifloxacin. The treatment sequence for clevidipine and placebo were randomised with a 1:1 ratio and administered single-blind (only subjects but not staff blinded to the treatment). Moxifloxacin was given as the last arm for each subject under open-label conditions.[9] The treatment periods were separated by 7 days to allow washout of the primary metabolite of clevidipine.

ECG data from the end of the therapeutic infusion phase and during the supratherapeutic infusion were used to assess the effects of clevidipine and the major metabolite at therapeutic and supratherapeutic concentrations, respectively. Post-infusion observations assessed effects during the rapid decrease in the parent drug concentration and the initial washout of the primary metabolite.

The study was executed with critical observations at correct times in relation to concentration maxima. An adequate number of subjects completed the crossover and moxifloxacin therapy, and the ECG dataset was complete. Moxifloxacin administration was associated with the expected rise of the mean delta-delta (dd)QTcF (QT corrected using the Fredericia formula) with the lower bound of its one-sided 95% CI greater than 0 msec, thus confirming the sensitivity of the assay. There was no evidence that either clevidipine or its major metabolite HI52/81, at therapeutic or supratherapeutic concentrations, caused prolongation of cardiac repolarisation. The results demonstrated that supratherapeutic concentrations of clevidipine and metabolite were not associated with increases of QTcF or QTcEi (QT corrected using exponential formula on individual data). In fact, statistically significant, albeit modest, decreases of QTcF and QTcEi were found. The maximal mean, control-subtracted changes of QTcF and QTcEi were less than five and the upper bounds of the one-sided 95% CI were less than 10 msec.

This was further confirmed by findings of minimal excesses during clevidipine treatment, compared to control, of QTc (interval from onset of QRS complex to end of T wave-corrected for rate) and ddQTc outliers, ST, T wave and U wave changes, and the absence of abnormal diagnostic changes. Most of the associated findings could be attributed to the higher heart rates during clevidipine therapy. The QTcB (interval from end of the P wave to the onset of the QRS corrected using the Bazett formula) results were essentially uninterpretable. Additional ECG findings, all control-subtracted, included the expected statistically significant HR rise maximal at 24.1 beats per minute (bpm), mild pulse rate (PR) prolongation maximal 13.2 msec, and minor QRS shortening reaching a minimum of -4.9 msec (p values of < 0.0001, 0.0013 and 0.0022, respectively). The results of the ECG analysis from the Main Study met all of the E14 criteria for a negative thorough QT/QTc Study.[10] This conclusion was achieved with strong statistical significance and positive assay sensitivity. No prolongation of cardiac repolarisation was associated with either clevidipine (at therapeutic and supratherapeutic concentrations) or its major metabolite H152/81.

[9] Moxifloxacin was used as the positive control as it is known to lead to prolongation of the QTc interval.
[10] International Conference on Harmonization (ICH) Guidance E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. E14 calls for a study design that will measure the drug's effect on QTc (QT corrected to allow comparison of QT measured at different heart rates), reporting the mean delta-delta QTc (ddQTc) and 95% upper confidence interval at each analyzed time point.

Pharmacodynamics in patients

Phase II studies in essential hypertension

The single-blind, study **SAD-0004** evaluated the dose-response relationship of clevidipine after IV administration (at dose rates 0.1, 0.2 and 0.6 μg/kg/min [0.48, 0.96, 2.88 mg/h]) in 13 patients with essential hypertension on oral therapy with β-blockers. The clevidipine infusion was administered in three steps and the infusion rates were adjusted to obtain a MAP reduction of 5%, 10% and 15% from baseline; then the dose rate was held constant for 12 minutes. A total infusion time including titration time was 67-174 minutes (1.1-2.9hours); ECG, BP, and HR were recorded before, during and after the study. Blood samples for determination of clevidipine were collected at appropriate intervals. The PK-PD relationship was evaluated by linear regression analysis of the percentage reduction in MAP and log dose and the corresponding log blood concentrations during each constant rate infusion. An average decrease in MAP of 5%, 10%, and 15% occurred at dose rates of 0.1, 0.2 and 0.6 μg/kg/min, respectively. The corresponding blood concentrations were 1, 4 and 12 nmol/L. These dose rates are much lower than those required in healthy volunteers to reduce MAP by 10%. This difference is in part due to the presence of a reflex increase in HR in normotensive volunteers, in whom the baroreflex is more powerful than in patients with essential hypertension on treatment with an oral β-blocker. In this study, there was conformity between the model-predicted $t_{1/2}$ of clevidipine (median 3.2, range 2.2-4.9 min) and time to recovery of 50% of the effect (t50) (median 4.5, range 1.7-9.8 min). The corresponding values for an 80% decrease in blood concentration and time to recovery of 80% of the effect were 7.4 minutes and 8.7 minutes, respectively. The rate of recovery was rapid regardless of the final infusion rate or the total duration of clevidipine administration.

Overall, results from this study show that clevidipine causes dose-dependent reduction in arterial blood pressure at dose range studied (15% reduction in MAP at 0.6 μg/kg/min or 2.88 mg/h) in patients with essential hypertension using oral beta-blockers concomitantly.

SAD-0010 was a randomised, placebo-controlled, single-blind, five-arm, three-way crossover study in 21 patients with moderate essential hypertension (seated systolic blood pressure [SBP]≥160 and DBP ≥100mmHg). All antihypertensive treatment was withdrawn at least one week prior to the first infusion of study drug. If the patient was treated with more than one antihypertensive drug, those were withdrawn gradually. Blood pressure was monitored regularly after the antihypertensive therapy had been withdrawn. Each patient received three out of five possible infusion rates of clevidipine or placebo on three separate study days. The target dose rates for clevidipine were 0.18, 0.91, 2.74 and 5.48 μg/kg/min (0.86, 4.37, 13.2, and 26.3 mg/h), respectively. The dose rates of clevidipine used in this study were selected to cover the anticipated dose rates in clinical use, that is, in perioperative control of blood pressure. The lowest dose rate used was assumed to give no or very low effect. An infusion rate of 0.91 ug/kg/min was assumed to give an adequate therapeutic effect, whilst the higher infusion rates were selected to be close to the maximal tolerable doses. The dose rates of clevidipine were increased slowly in a stepwise manner until the target dose rates were achieved to specifically allow baroreceptor adaptation and to achieve an optimal effect on blood pressure with minimal reflexogenic tachycardia.

After completing the first treatment arm, patients were crossed over to the next treatment arm within 2-7 days. Each infusion lasted 240 minutes (a dose titration phase lasting for 120 minutes preceded an infusion of clevidipine at a target dose rate for 120 minutes). This was followed by a wash-out period of 120 minutes. Venous blood samples for determination of clevidipine and its enantiomers were collected at appropriate intervals. A one-compartment model was fitted to each individual's blood concentrations obtained during the target dose

rates of 0.18 and 0.91 µg/kg/min (0.9 and 4.4 mg/h) and a two compartment model was fitted to each individual's blood concentrations obtained after the target dose rates of 2.74 and 5.48 µg /kg/min (13.2 and 26.3 mg/h), respectively. An additional non-compartmental analysis was also performed to determine clearance (CL) and the Css of clevidipine. The dose rates for the individual enantiomers were assumed to be half the dose rates of the racemate of clevidipine.

During steady state infusion, dose-dependent reductions in mean SBP, DBP and MAP were observed. A modest increase in HR was also noted**.** However, even at the highest dose rate, the increase in heart rate was small, as compared to the tachycardia observed when clevidipine was given to healthy volunteers. This can probably be attributed to the differences in the study designs as this study allowed a baroreflex adaptation by inducing stepwise reductions in blood pressure, whereas this was not the case in the previous studies in healthy subjects, in which clevidipine caused a sudden reduction in blood pressure. The maximal reduction of MAP was about 30% and the blood concentration producing half the maximal effect, that is, concentration of drug producing half of maximum effect, was approximately 25 nmol/L. The corresponding value for ED_{50}, that is, the dose rate producing half the maximal effect, was 1.5 µg/kg/min (7.2 mg/h). Furthermore, mean values of MAP and recovery times on completing drug administration showed dose-related greater reductions in mean MAP and longer times to recovery with clevidipine dose rates of 0.91, 2.74 and 5.48ug/kg/min compared with placebo and clevidipine 0.18ug/kg/min. Additionally, clevidipine induced dose dependent reductions in SBP and DBP. MAP and HR were back to pre-dose values 15minutes after the infusion of clevidipine was stopped.

TMC-CLV-06-01 was a Phase IIb, randomised, single-blind, placebo-controlled study in 61 patients with mild to moderate hypertension (Table 5)**.** Patients withdrew from their oral anti-hypertensive medications for 8 to 14 days prior to any clevidipine administration. In the untreated state, patients exhibited SBP ≥140 mmHg and <200 mmHg and/or DBP ≥95 mmHg and <115 mmHg; HR <120 beats per minute. BP and HR measurements were taken at adequate time-points. Baseline demographics and disease characteristics were similar between different treatment groups. The clevidipine and placebo treatment groups were similar with regards to the most commonly prescribed medications administered prior to the study start and also the commonly prescribed concomitant medications administered during the study**.** All patients receiving oral antihypertensive medications prior to the study start withdrew these treatments for at least 8 to 14 days prior to the start of clevidipine dosing.

Table 5: Details of Study TMC-CLV-06-01: Phase IIb PK- PD study in patients with essential hypertension

Study design	**Subjects**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase IIb, randomised, single-blind, multicentre, placebo-controlled, parallel group study. Treatment duration was 72	N=61 pts with mild/ moderate essential hypertension. Age: 21-78yrs, mean=55 yrs Sex:	Clevidipine (0.5 mg/mL in 20% lipid emulsion) in 50 mL bottles administered intravenously. Placebo (Intralipid: 20% lipid emulsion) was administered intravenously in the same fashion as clevidipine. Within each dosing cohort, 10 patients were to be randomized to receive clevidipine and three to receive placebo.	Primary endpoint: Mean percent change in SBP from baseline over the 72 hour Rx period Secondary endpoints: Mean percent change in SBP from baseline over the first 4 hours post study drug infusion; Blood concentration of clevidipine over the 72 hour treatment period through 60 minutes post	Forty-three of the 61 patients enrolled experienced one or more AEs. Overall, 112 AEs were reported: 84 AEs following administration of clevidipine, and 28 AEs following placebo. The most common AEs reported across treatments and dose levels were headache,

hours at the target dose. Patients were followed for 7 days from initiation of study drug administration. 3 sites in USA.	40M:21F Race: White=43 Black=18 Hispanic=9 Others=1.	Clevidipine 2.0 mg/h, n=10 Clevidipine 4.0 mg/h, n=10 Clevidipine 8.0 mg/h, n=18 Clevidipine 16.0 mg/h, n=10 Placebo, n=13. Clevidipine was administered at an initial infusion rate of 2.0 mg/h to patients in each cohort and force titrated by doubling increments every 3 minutes to the target dose for Cohorts 2, 3 and 4. The target dose was maintained continuously for 72 hours.	study drug infusion; Relationship between the time-matched, placebo-adjusted mean percent change in SBP from baseline and the mean blood concentration of clevidipine over the 72 hour treatment period through 60 minutes post study drug infusion. Safety of a prolonged infusion of clevidipine (72 hours) assessed according to clinical laboratory parameters, HR, ECGs and adverse events (AEs).	infusion site reaction, infusion site swelling, and infusion site erythema. There was no apparent dose or treatment-related differences in AE incidence, description, severity, or duration between the clevidipine dose cohorts. No deaths or SAEs. No clinically relevant changes in ECG or laboratory parameters.

All active treatment cohorts showed a larger percentage decrease from baseline in SBP as compared to placebo, however Cohort 1 (clevidipine 2.0 mg/h) shows a lower percent change in SBP from baseline as compared to placebo than Cohort 2 (clevidipine 4.0 mg/h). For the remaining Cohorts 3 and 4 (clevidipine 8.0 and 16.0 mg/h), the decline in percent change from baseline SBP was dose dependent. The change from baseline SBP was observed to be greater in Cohort 4 (16mg/h) compared to all other cohorts. A rapid onset of drug effect (decrease in SBP from baseline) was seen for all dose levels of clevidipine.

There was a trend for a greater percent change from baseline SBP with increased steady state blood concentrations of clevidipine, although there was substantial variability. The concentration-response curve was fairly shallow in nature**.** Over the range of Css values evaluated, there was no apparent maximum response in change from baseline SBP.

Overall, no tolerance was developed during continuous prolonged clevidipine infusion for 72 hours, with the decrease from baseline in SBP being maintained at relatively constant levels throughout the infusion at all four dose levels. There was no evidence of rebound hypertension following termination of the clevidipine infusion at all 4 clevidipine doses with SBP returning to baseline following cessation of treatment.

Phase II studies in perioperative hypertension

SAD-0003 was an open-label, randomised, multicentre, placebo-controlled study (Table 6) in 91 post-cardiac surgical patients to evaluate the dose-response and pharmacokinetics of clevidipine following IV infusion of 0.05, 0.18, 0.32, 1.37, 3.19 and 9.58 μg/kg/min (0.2, 0.86, 1.54, 6.58, 15.3, and 45.9 mg/h). During surgery, anaesthesia was administered according to the discretion of the investigators. Postoperatively in the intensive care unit (ICU), sedation with propofol was given according to the general hospital standard. All antihypertensive therapy must have been stopped five minutes prior to randomisation. Beta-blockers were allowed, the morning of surgery. A Swan Ganz catheter was used to determine the central hemodynamic variables. Standard equipment was used for MAP-recordings (i.e. invasive techniques with a radial artery catheter). Pharmacokinetics of clevidipine were determined by the population based modelling (67 patients) approach while the PD effect of clevidipine was measured in terms of the percentage decrease in MAP as a function of clevidipine blood concentration.

The response rate was statistically significantly ($p \leq 0.004$) greater than placebo for all clevidipine doses $\geq$0.32ug/kg/min (0%, 9%, 31%, 60%, 75%, 95% and 100% in the placebo,

clevidipine 0.05, 0.18, 0.32, 1.37, 3.19 and 9.58 µg/kg/min groups, respectively) (Table 7). Hence, 0.32ug/kg/min appeared to be the minimum effective dose (MED) for clevidipine in terms of responder analysis (Figure 2)**.** Increasing dose rates of clevidipine (0.05-9.6 µg/kg/min or 0.2-46.8 mg/h), caused dose-dependant reduction in MAP with no change in HR (Figure 3)**.** There was a statistically significant difference in MAP, SBP**)** and DBP between all doses of clevidipine and placebo ($p<0.05$), except for clevidipine 0.05 ug/kg/min ($p>0.05$).

Table 6: Details of Study SAD-0003 Phase IIb dose-response and PK study in patients with essential hypertension

Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Safety/AEs
Phase II, randomised, open-label, multicentre, placebo-controlled, study. Duration of Rx was 122 minutes with a subsequent optional maintenance Rx phase with clevidipine up to 12 hours at a dose level that was needed to maintain a MAP of 70-95 mmHg. At 6 centres in USA.	N=91 post-cardiac surgical (CABG and/or valve surgery) pts with MAP >90mmHg at 2 consecutive readings. Age: 35pts aged 50-64yrs & 41 pts >64yrs. Sex: 73M:18F Race: Caucasian=72 Black=9.	Clevidipine (0.5 mg/mL in 20% lipid emulsion) in 50mL bottles administered intravenously. Placebo (Intralipid®: 20% lipid emulsion) was administered intravenously in the same fashion as clevidipine. Clevidipine 0.05ug/kg/min, n=11 Clevidipine 0.18ug/kg/min, n=13 Clevidipine 0.32ug/kg/min, n=10 Clevidipine 1.37ug/kg/min, n=12 Clevidipine 3.19 ug/kg/min, n=20 Clevidipine 9.58ug/kg/min, n=14 Placebo, n=11. Clevidipine was administered at an initial infusion rate of 2.0 mg/h to patients in each cohort and force titrated by doubling increments every 3 minutes The target dose was maintained for 122mins with option to continue till 12hrs if required.	Primary- response rate of each dose level of clevidipine and placebo, where a responder is defined as a patient having at least a 10% reduction from baseline-MAP during the first 122minute-Rx phase, while still on the randomised dose. Secondary- mean change from baseline in MAP, SBP, DBP and HR PKs in 67 pts: The blood samples were collected at 10, 18, 33, 48, 68 and 88 minutes after the start of fixed dose infusion. after stop of infusion at times: 30 seconds, 1, 1.5, 2, 3, 6, 12, 18 and 20 minutes (i.e., during wash-out)	All pts reported AEs; 1256 AEs reported by all 91 pts. SAEs= (15/91) and discontinuations due to AEs= 21 (23%) with no sig diff b/w Rx groups. Highest dose rate of clevidipine (9.58ug/kg/min) led to hypotension resulting in discontinuation of study therapy occurred in 28%of the patients. No deaths. No clinically relevant changes in ECG or laboratory parameters.

Table 7: Study SAD-0003 – Response rates of the six doses and placebo

Randomised dose	Non-responders n (%)	Responders n (%)	p-value, comparison with placebo
Placebo	11 (100)	0 (0)	
0.05 µg/kg/min	10 (91)	1 (9)	0.500
0.18 µg/kg/min	9 (69)	4 (31)	0.067
0.32 µg/kg/min	4 (40)	6 (60)	0.004
1.37 µg/kg/min	3 (25)	9 (75)	<0.001
3.19 µg/kg/min	1 (5)	19 (95)	<0.001
9.58 µg/kg/min	0 (0)	14 (100)	<0.001

Figure 2: Study SAD-0003 Dose rate and reduction in MAP

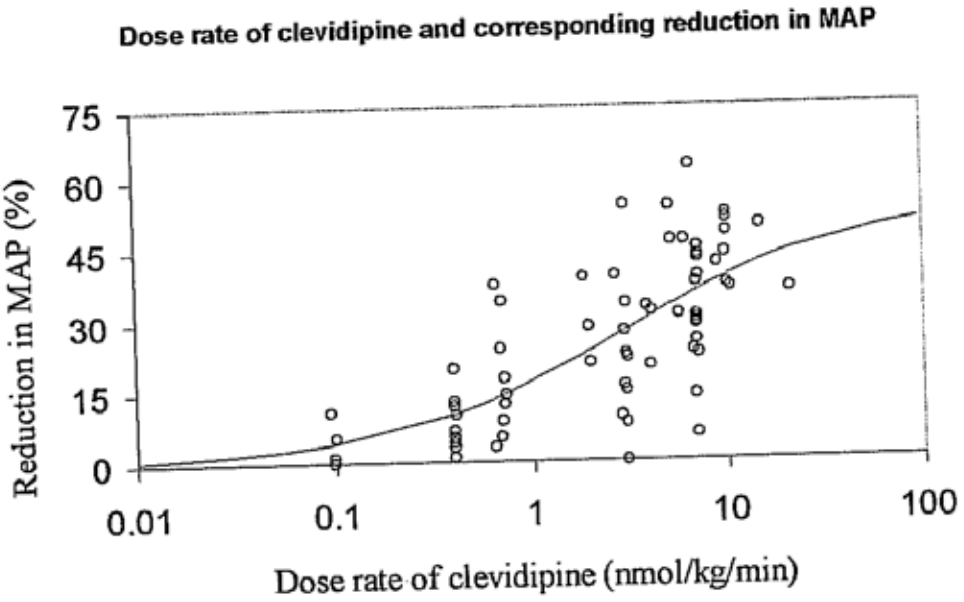
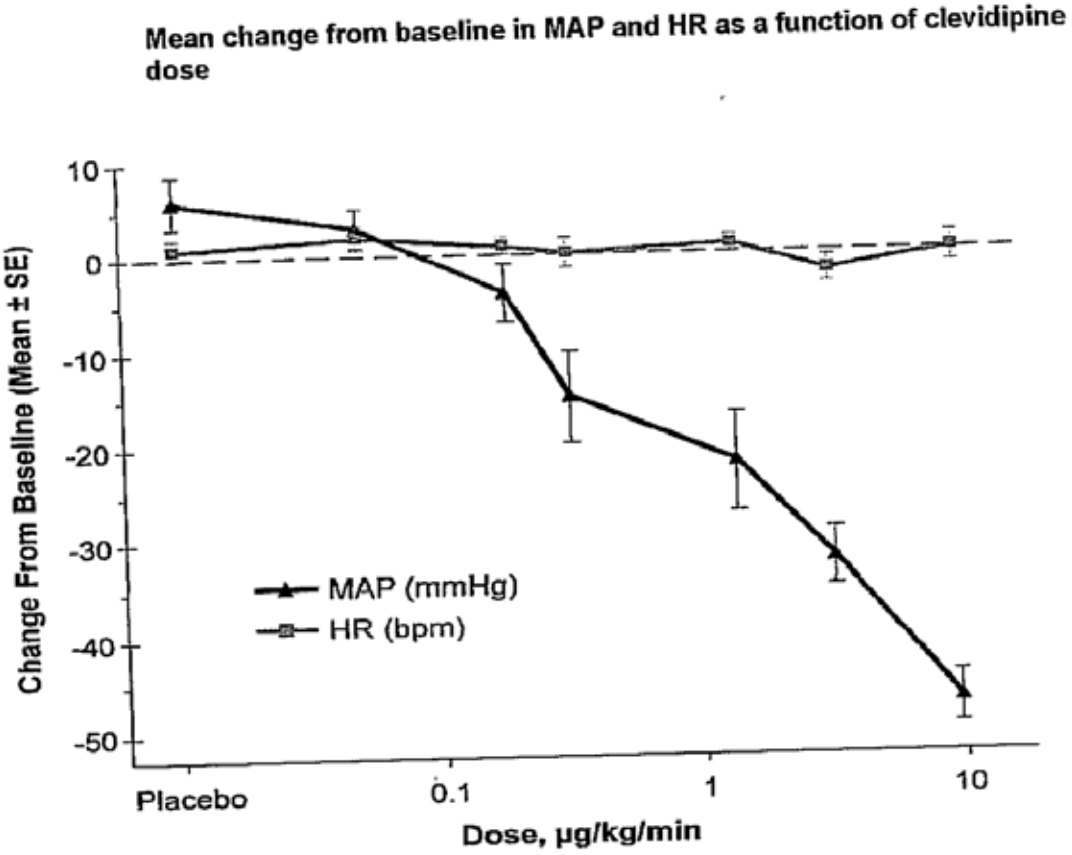


Figure 3: Study SAD-0003



Furthermore, clevidipine (0.05-9.6 μg/kg/min or 0.2-46.8 mg/h) did not appear to produce any consistent, clinically relevant changes in central hemodynamic parameters of pulmonary capillary wedge pressure (PCWP), pulmonary arterial pressure (PAP), central venous pressure (CVP), pulmonary vascular resistance (PVR), stroke volume index (SVI) and cardiac index (CI). The decrease in MAP occurred without affecting HR, cardiac index or cardiac filling pressure.

The percentage of patients that escaped to the next higher dose arm was 80%, 45%, 15%, 30% and 8% for placebo, clevidipine 0.05, 0.18, 0.32 and 1.37ug/kg/min, respectively. This endorses a dose-blood pressure reduction response relationship of clevidipine, which was further supported by the large proportion of patients who escaped downwards to the next lower dose arm from the 3.19 and 9.58 ug/kg/min randomised dose arms (75% and 93%, respectively). Based on the large proportion of patients who escaped from the highest dose arm tested it is concluded that the upper limit of the therapeutic dose range of clevidipine is 3.19 ug/kg/min. Highest dose rate of clevidipine (9.58ug/kg/min) led to hypotension resulting in discontinuation of study therapy in 28% of the patients. Hence, the highest recommended dose rate in further studies was 3.19ug/kg/min.

Minimum effective dose (MED) rate of clevidipine with regard to the MAP responder analysis was found to be 0.32 μg/kg/min (1.5 mg/h) while the lowest effective dose rate with regard to lowering blood pressure as compared to placebo was found to be 0.18 μg/kg/min (0.9 mg/h).

Effect was expressed as percent change in MAP in the PK/ PD modelling. By utilising an Emax model in analysing the relationship between decrease in MAP and blood concentration, the maximal effect was 24.8% with an EC50 value of 6.25 nmol/l. Corresponding data obtained in the analysis of the relationship between effect and dose-rate were Emax: 54.2 % and ED50: 1.3 ug/kg/min. The lower Emax in the former analysis may have been influenced by the design of the study, ie patients randomised to higher dose rates escaped frequently out of the study due to hypotension before blood samples were actually drawn. The study design thus essentially precluded accurate analysis of the maximal effect when relating effect versus blood concentration. However, when all 91 patients were included and effect was related to actual dose rate, a reasonable maximal effect was obtained.

The evaluator commented that results from this study provided evidence that the therapeutic dose-rate for clevidipine suitable for a clinical setting ranged from 0.18 to 3.19 μg/kg/min (0.9 mg/h to 15.3 mg/h).

SAD-0005 was a Phase II, open-label study which compared the effects of clevidipine and sodium nitroprusside (SNP) on central haemodynamics, myocardial blood flow and metabolism in 18 postcardiac surgical patients (Table 8). At randomisation, the patients were haemodynamically stabilised, mechanically ventilated and continuously sedated. The second SNP challenge (SNP2) was made with the aim of reconstructing the results obtained during first administration of SNP (SNP1) in order to avoid any misinterpretation of clevidipine results as being due to a gradual and time-dependent change in baseline conditions, a situation that may occur in the early phase following coronary artery bypass graft (CABG) surgery. There were 2 study phases: constant rate infusion and dose-response phases**.**

Constant rate infusion part of the study consisted of three 10-minute constant rate infusion periods with SNP, clevidipine and SNP with 10-minute wash-out periods; during the wash-out period, infusion of the drug for the next 10-minute period was started slowly until a constant rate infusion was reached, that is, when MAP was maintained at a level of 70-80 mmHg. Blood pressures, central haemodynamics, myocardial blood flow and metabolism

were measured at the start of study (during the first SNP infusion) and after 10minutes of a constant rate infusion of SNP, clevidipine and SNP. Peripheral arterial and venous blood samples for analyses of the clevidipine concentrations were taken in conjunction with the haemodynamic recordings, and during washout. The mean final dose rates to achieve and maintain a MAP of 70-80mmHg were 1.14, 0.68 and 2.27ug/kg/min for SNP1, SNP2 and clevidipine, respectively**.**

Table 8: Details of Study SAD-0005 Phase II, study comparing pharmacodynamics of clevidipine and sodium nitroprusside (SNP)

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase II, randomised, open-label study. 13 patients in constant infusion part of study and 9 patients in dose-response part of the study. One site in Sweden. .	N=18 post-cardiac surgical (CABG) pts who had taken beta-blockers prior to surgery.. Age: 49-80yrs, mean=65yrs. Sex: 17M:1F Race: Caucasian=18. Only 13 pts received Rx in first part of study and 9 of these pts continued onto the dose-response phase.	Clevidipine (0.5 mg/mL in 20% lipid emulsion) in 50mL bottles administered intravenously. Constant infusion phase: (3 10-min periods with 10min washout b/w treatments)- started with maximal infusion rate of clevidipine 0.23 ug/kg/min and the maximal infusion rate was 22ug/kg/min; the infusion rate of clevidipine was increased in steps and kept constant when a MAP of 70-80 mmHg was achieved. Infusion rate of SNP was adjusted according to the need of the patient to maintain a MAP of 70-80mmHg. Dose response phase:- clevidipine was given in step-wise increasing doses of 0.37, 0.75, 1.5 and 3ug/kg/min.	Recordings of central haemodynamics. myocardial blood flow and metabolism at a MAP of 70-·80 mmHg. Pharmacokinetic profile of clevidipine. and elucidation of which infusion rates of clevidipine to be required to maintain a MAP of 70-80mmHg. Safety	Only 14 male pts received drug and included in safety analysis. 5/14 reported AEs of which atrial fibrillation was most common. 1 SAE No deaths. No clinically relevant changes in ECG or laboratory parameters.

HR was lower with clevidipine in comparison to SNP, although the difference was small and not tested for significance. SV was significantly higher and CO was higher with clevidipine, probably due to a more pronounced dilatation of svstemic resistance vessels as reflected by lower systemic vascular resistance (SVR) and less systemic vascular resistance index (SVR_{index}) and less pronounced or no effect on venous capacitance vessels as reflected by maintained filling pressures (CVP and PCWP)**.** Thus clevidipine seems to be a more efficient afterload-reducing compound compared to SNP. Furthermore, the effect on pulmonary vascular resistance (PVR) was less pronounced with clevidipine, which probably makes clevidipine a less potent vasodilator of the pulmonary circulation compared to SNP.

There were no statistically significant differences between the first and second infusions of SNP in the 4 main haemodynamic variables that were tested (PCWP, SV, SVR and CVP**)**. However, there were statistically significant differences between SNP1 and clevidipine in favour of clevidipine on all four variables tested (Table 9).

At equipotent MAP levels, mean values of coronary sinus flow increased during clevidipine infusion as compared to SNP, but the flow in the great cardiac vein did not. Furthermore, there were no statistically significant differences in myocardial lactate uptake or myocardial oxygen extraction between the two drugs, indicating that the direct vasodilatory effect of

clevidipine on coronary resistance vessels was not different from that seen with SNP and that both agents were equivalent with respect to myocardial lactate metabolism.

The PD evaluation of clevidipine measuring the reduction in SVR used an Emax model which was fitted to the pooled data of all individuals (dose-response part), correlating the observed arterial blood concentrations with the percent reduction in SVR_{index} from control value. According to the derived model, the maximum reduction in SVR_{index} that could be achieved with clevidipine was calculated to be 32% of its control value (Emax). Half of the maximum reduction in Emax was attained at 29 nmol/L (EC50). Based on the mean CL of clevidipine, a steady state level equal to EC_{50} should be obtained at a dose rate of 0.6 µg/kg/min or 2.88 mg/h. However, the precision of these estimates was affected by relatively few observations at high concentrations (> 100 nmol/L), variation in base line and also the interindividual variations in dynamic response.

Table 9: Study SAD-0005 – Mean difference between SNP 1 and Clevidipine at Constant Rate Infusion

SNP 1 vs clevidipine		**95% CI**		
Variable	**Mean difference**	**Lower**	**Upper**	**p-value**
PCWP (mmHg)	1.62	0.53	2.71	0.0073
SV (mL/beat/m^2)	8.00	3.80	12.20	0.0014
SVR (dynes x sec x cm^{-3}	-101.46	-181.46	-21.46	0.0172
CVP (mmHg)	1.62	0.99	2.25	0.0001

The dose-response part of the study included controlled step-wise dose-titration of four fixed doses of clevidipine given to nine patients after the second SNP infusion to evaluate the dose-response relationship of clevidipine. During this phase of the study, clevidipine showed a similar haemodynamic pattern to that of SNP. With increasing doses of clevidipine, SVR was significantly reduced, mean values of MAP were reduced and SV was increased significantly, indicating afterload reduction. Mean values of CO and filling pressures remained unchanged. No reflex tachycardia was seen which is different from what has been demonstrated with other short-acting calcium antagonists and also with clevidipine in conscious healthy volunteers**.** Mean values for coronary sinus vessels and great cardiac vein flow were unchanged, while myocardial oxygen extraction was significantly decreased by clevidipine. Myocardial lactate uptake did not change significantly with increasing doses of clevidipine, although mean values were reduced as were mean values of myocardial lactate extraction. However, no lactate production was present in individual patients. These results indicate a dose-dependent direct vasodilating effect on the coronary resistance vessels with no negative effect on myocardial lactate metabolism.

The primary objectives of **SAD-0006, a** Phase II, open-label study in 17 patients undergoing CABG were to identify the dose rate of clevidipine required to lower high blood pressure during the pre-bypass phase and the hypothermic period of the bypass phase during cardiac surgery and to investigate safety during these periods (Table 10). The secondary objectives were to determine the pharmacokinetics and compare the half-life of clevidipine during the pre-bypass phase and the hypothermic period of the bypass phase.

Recommended dose rate range was 1.4 -3.2 ug/kg/min allowing both a lower and a higher dosage if needed. The infusion of clevidipine was given in a dose sufficient to produce 20% reduction in MAP (from 90-95mm Hg to 70-75mm Hg) and mean perfusion pressure (MPP) (from 75-80mm Hg to 55-60mm Hg) during pre-bypass and during bypass hypothermia,

respectively. Dose rate was adjusted until the desired reduction of the ratio MAP/MPP was achieved during the pre-bypass and bypass period and then the dose rate was held constant for ten minutes. Administration of clevidipine was continued if needed during the post-bypass period and/or in the intensive care unit (ICU) up to 12 hrs after start of infusion. An escape design was included in the study design. Escape to other treatment (sodium nitroprusside, SNP) was to be performed if MAP/MPP (rewarming) reached a pre-defined level or if blood pressure was not controlled by increasing doses of clevidipine. Mean values indicate that the target blood pressure was reached following clevidipine infusion pre-bypass and during bypass, although individual values suggest a large interindividual variation in the dose rate and response**.** The median of the individual pressure reached during the constant infusion was 72 (C.I. 68-78) mm Hg during pre-bypass and 55 (50-62) mm Hg during bypass. This was achieved by median dose rates of 2.24 (C.I. 1.6 - 2.53) ug/kg/ min in pre-bypass and 1.20 (0.93 -1.60) ug/kg/min in the bypass phase**.** There were too few observations to enable calculation of central hemodynamic parameters such as CO, CVP, PAP and PCWP.

Table 10: Details of Study SAD-0006 Phase II, study in patients undergoing cardiac surgery

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase II, randomised, open-label study. One centre in the UK. .	N=17 pts undergoing cardiac surgery (CABG) & developed high BP during pre-bypass &/ or during hypothermic phase of bypass surgery. Age: 44-76yrs, mean=62yrs. Sex: 14M:3F Race: Caucasian=17. 17 pts evaluated in pre-bypass phase & 8 evaluated in bypass phase of surgery. 11 pts were on oral beta-blockers, with last dose received on morning of surgery.	Clevidipine (0.5 mg/mL in 20% lipid emulsion) in 50mL bottles administered intravenously. Recommended dose rate range was 1.4 -3.2 ug/kg/min (3-7 nmol/ kg/min), allowing both a lower and a higher dosage if needed. The infusion of clevidipine was given in a dose sufficient to reduce MAP from 90-95mm Hg to 70-75mm Hg during pre-bypass and mean perfusion pressure (MPP) from 75-80mm Hg to 55-60mm Hg during bypass hypothermia, aiming at a 20 per cent decrease of MAP and MPP. Dose rate was adjusted until the desired reduction of MAP/MPP was achieved during the pre-bypass and bypass period, respectively. Then the dose rate was held constant for ten minutes. Administration of clevidipine was continued if needed during the post-bypass period and/or in the intensive care unit (ICU) up to 12 hrs after start of infusion.	Blood pressure (BP, invasive) and heart rate (HR) were continuously monitored for 15 hours from the start of the anaesthesia induction. A Swan Ganz catheter was used to measure CO, CVP, PAP and PCWP. The stroke volume (SV), cardiac index (Cl), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were also calculated. Primary endpoint- mean dose rate required to maintain BP during pre-bypass and hypothermic phase of bypass surgery. Secondary- Pharmacokinetics- t1/2 and clearance during pre-bypass and bypass surgery. Safety.	One pt (on 2.7ug/kg/min) discontinued Rx due to AE (hypertension and bleeding) and was put on SNP. No SAEs or deaths. No clinically relevant changes in ECG or laboratory parameters.

The evaluator commented that, overall, the mean dose rate required to control BP during pre-bypass (2.17 µg/kg/min or 11 mg/h) was higher than that required to control BP during bypass (1.26 µg/kg/min or 6 mg/h), which was most likely due to reduced clevidipine clearance during bypass hypothermia.

Summary of pharmacodynamics

Following a 20 minute constant infusion of clevidipine (3.2 μg/min/kg; 16 mg/h) in healthy volunteers, the time to onset of effect was less than 5 minutes from the start of clevidipine infusion to the attainment of maximal effect on haemodynamic parameters. Similarly, in patients with mild to moderate hypertension (TMC-CLV-06-01), administration of clevidipine (2.0, 4.0, 8.0 and 16.0 mg/h). for 72 hours led to rapid onset of drug effect (3%-18% decrease in SBP from baseline within 10 minutes) for all dose cohorts followed by a rapid return (within 10 minutes) to baseline SBP on cessation of treatment. In study TMC-CLV-06-02), clevidipine was administered to patients with severe hypertension for up to 60 hours and the SBP was successfully decreased to the initial pre-specified SBP target range within 30 minutes of initiation of clevidipine infusion (median time was 10.9 minutes). Overall, clevidipine demonstrates a rapid onset of action (2-10 min) in all hypertensive patients.

The time to recovery of the haemodynamic effect is short, and in most studies the SBP, MAP and HR return to baseline values within minutes after discontinuation of clevidipine infusion.

The therapeutic dose-rate range for clevidipine suitable for a clinical setting ranged from 0.18 to 3.19 μg/kg/min (0.9 mg/h to 15.3 mg/h) (study SAD-0003).

The mean dose rate required to control BP during pre-bypass (2.17 μg/kg/min or 11 mg/h) was higher than that required to control BP during bypass (1.26 μg/kg/min or 6 mg/h), which was most likely due to reduced clevidipine clearance during bypass hypothermia (study SAD-0006).

There is a close visual correlation between the arterial blood concentrations and dynamic response during and after the short infusion of clevidipine. This correlation between concentration and response, taken together with the rapid clearance of this agent, suggests that clevidipine can be rapidly titrated to the desired effect (study SAD-0018).

Clevidipine rapidly reduced MAP and induced a systemic, pulmonary and coronary vasodilation with no effect on venous capacitance vessels or HR. Cardiac output and stroke volume increased by 10%. Results of study SAD-0005 suggested a dose-dependent vasodilatory effect on coronary vessels with no negative effect on myocardial lactate metabolism.

Pharmacokinetics

Introduction

The nonclinical studies and the early clinical studies utilized a gas chromatography – mass spectrometry (GC-MS) method for clevidipine, and a liquid chromatographic method with fluorescence detection (LC-Fluor) for the inactive M1 (H152/81) metabolite. More recent clinical studies used a liquid chromatography – mass spectroscopy/mass spectroscopy (LC/MS/MS) assay to determine clevidipine and the M1 metabolite in blood (with a sensitivity of 0.2 ng/mL for clevidipine and 20 ng/mL for the M1 metabolite).These assay methods were developed and validated by AstraZeneca. These methods provide sufficient sensitivity and selectivity for the determination of clevidipine and its major but inactive metabolite in samples from pharmacokinetic and clinical studies.

Cleviprex is formulated as a ready to use, sterile, white, opaque oil-in-water emulsion for intravenous administration via syringe or volumetric pump. The active ingredient, clevidipine butyrate (0.5 mg/mL), is formulated as a lipid emulsion in 20% soybean oil (composition similar to Intralipid) and stabilized with purified egg yolk phospholipids. Both the drug product and drug substance formulations have been used consistently across the clinical

development program, eliminating the need for the sponsor to conduct relative bioavailability or bioequivalence studies. An absolute bioavailability study comparing clevidipine's lipid emulsion and an aqueous based formulation (water or ethanol) has not been conducted due to clevidipine's insolubility in water and its sparing solubility in 99.5% ethanol.

Studies using human biomaterials (in vitro studies)

A series of *in vitro* experiments in whole blood to evaluate effect of clevidipine on P450 enzymes, metabolic interaction of clevidipine with other drugs, influence of deficiency of pseudocholinoesterase on elimination rate of clevidipine, and the effect of temperature and dilution on $t_{1/2}$ of clevidipine were conducted.

Clevidipine produced significant induction of CYP3A4 but not CYP1A2 and CYP2C9 at 10uM and 100uM concentrations. Furthermore, clevidipine inhibited CYP2C9, CYP2C19, CYP2D6 and CYP3A4 catalytic activities with IC_{50} values of 4.4, 2.5, 72 and 8.4uM, respectively; the catalytic activity of CYP1A2 and CYP2E1 was inhibited by less than 50% at 300uM, the highest concentration of clevidipine examined**.** Although clevidipine did cause induction and inhibition of certain CYP450 isozymes, the concentration values of both clevidipine and its major metabolites were at least 10 times higher than the highest clevidipine concentration typically seen in the clinic. Therefore it appears unlikely that clevidipine or its metabolites will cause cytochrome P450 related drug interactions when used in the dose range required to manage hypertension in humans.

Report 1253 evaluated the effect of phenotypically abnormal plasma pseudocholinesterase activity on the *in vitro* hydrolysis rate of clevidipine in fresh blood and plasma from human subjects. This was determined by the rate of hydrolysis of clevidipine into its primary metabolite, H152/81, in fresh blood and plasma from subjects phenotypically homozygous (having identical genes at one or more loci) and heterozygous (having different genes at one or more loci) for the atypical plasma cholinesterase gene. Results suggest that pseudocholinesterases may play a role in the elimination of clevidipine, and that genetic defects in the expression of this enzyme may result in some prolongation of the half-life**.** However, considering the very short half-life of the drug and that the effect of the drug can easily be titrated, this prolongation is not likely to be of any clinical importance.

The objective of study 1169 was to determine the rate and degree of hydrolysis of clevidipine into its primary metabolite H152/81 in fresh blood at three different temperatures and in diluted blood from humans of both genders. Results from this study show that clevidipine $t_{1/2}$ is temperature dependant and that clevidipine is quantitatively transformed to the inactive metabolite H152/81 by cleavage of the ester group. The *in vitro* $t_{1/2}$ of clevidipine was increased at lower temperatures, as would be expected of a drug metabolised by blood esterases; the clevidipine $t_{1/2}$ *in vitro* was 6 minutes at 37°C, 11 minutes at 30.5°C and 40 minutes at 18°C. Dilution of the blood with an equal volume of Ringer-glucose solution did not affect the *in vitro* $t_{1/2}$ of clevidipine.

Pharmacokinetics in healthy subjects

The pharmacokinetic (PK) and pharmacodynamic (PD) data of clevidipine in healthy volunteers were derived from 4 clinical trials **(SAD-0001, SAD-0002, SAD-0018 and TMC-CLV-05-01)** in which 104 volunteers participated. The doses of clevidipine administered in these studies ranged from 0.5 to 21.6µg/kg/min (2.4 to 103.7 mg/h for 80 kg subject) and the length of infusions ranged from 20 min to 24 h. The pharmacokinetics was evaluated using compartmental and non-compartmental analysis.

In early clinical trials, only venous blood samples for determination of PK parameters were collected. However, the first study in patients showed a marked difference between arterial

and venous blood concentrations. In further studies in which both arterial and venous blood concentrations have been determined during clevidipine infusion, the arterial blood levels have consistently been approximately twice of those found in venous blood. Also, during the initial infusion period (but not at steady state), the arterial blood concentration has been shown to be a better predictor of the haemodynamic response in healthy volunteers than the venous concentration. The difference between arterial and venous blood concentration indicates an extensive and very rapid metabolism of clevidipine in the blood and in the extravascular tissues.

SAD-0001

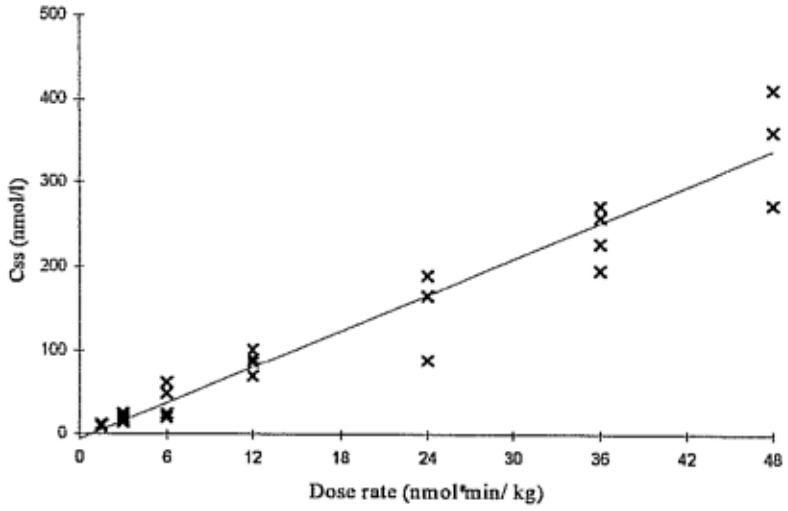
The primary objective of the randomised, Phase II, single-blind study SAD-0001 was to investigate the tolerability and safety of clevidipine after short-term (20 min IV infusions of gradually increasing IV doses to 23 healthy subjects. The secondary objective was to obtain a preliminary assessment of clevidipine PK in healthy volunteers. Clevidipine was administered in the dose range of 0.05 to 21.9µg/kg/min (0.24-105.1 mg/h) in following increasing dose steps: 1/50, 1/25, 1/12, 1/4,1/2,1,2,4,6 and 8 times the assumed therapeutic dose, which was 6 nmol/kg/min. The treatment was stopped at 48 nmol/kg/min (105mg/hr) when a predetermined safety endpoint: heart rate (HR) above 120 beats/minute was reached. For the first two dose steps the infusion were given to three subjects and for the consecutive dose steps to five subjects. Placebo was administered to one of the subjects in each dose step. Blood samples were taken for estimation of drug concentrations before, during and after the infusion. Electrocardiogram (ECG), blood pressure (BP) and HR were followed before, at different times during the infusion and for at least 4 hours after the infusion. BP and HR were also measured continuously with a non-invasive method. All subjects returned to the laboratory 3 (2-5) days after the drug infusion for safety follow-up. Adverse events were recorded throughout the study. The study was conducted from 9/8/1995 to 19/9/1995 and involved 25 healthy male subjects.

There was a linear relationship between the dose and the blood concentration of clevidipine (H 324/38) during steady state (Figure 4**).** Clearance of clevidipine was high (0.1 to 0.2 l/kg/min) and independent of dose rate**.** The reason for the rather large variation in blood concentration at each dose level was probably related to technical difficulties in rapid blood sampling, which was required to enable complete inhibition of blood esterases, which will otherwise also hydrolyse H 324/38(clevidipine) *in vitro*. The volume of distribution and half-life of H 324/38 could not be estimated with accuracy due to the assay limit of quantitation of 5nmol/l. However, since the blood sampling period extended over eight hours it was possible to determine the half-life of the metabolite H 152/81. The pharmacokinetics of H 152/81 determined in this study correspond well with those reported in SAD-0002, where blood sampling was continued for 32 hours.

Results from this study indicated that clevidipine shows a linear relationship between blood concentration and dose rate over the range 1.5 - 48 nmol/kg/min (3.2 -105.1 mg/h) and has a high clearance with extremely short $t_{1/2}$.

Figure 4: Study SAD-0001

Figure 4: Blood concentration during steady state vs. dose rate calculated by a linear regression analysis.



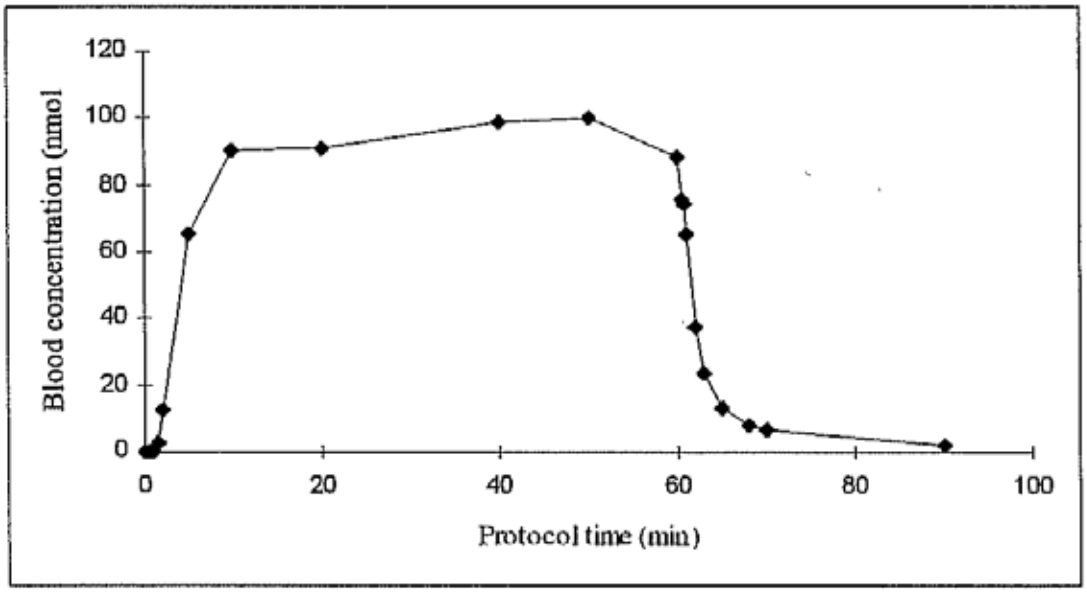
Line fitted C_{ss} = -5.45 + dose rate*7.18

SAD-0002

The open-label, single dose study SAD-0002 evaluated the PK, metabolism and rates and routes of excretion of clevidipine in 8 healthy male subjects after IV administration of clevidipine (12 nmol/kg/min; 5.42 µg/kg/min or 26.26 mg/h) containing a trace amount of 3H clevidipine during 1 hour as a constant IV infusion. Frequent blood samples were taken for estimation of drug blood concentrations before infusion and up to 32 hours after start of infusion. Urine and faeces were collected up to 168 hours after start of infusion. ECG, BP and HR were followed before, during and after the infusion. The noncompartmental and the model-dependent methods used for calculating PK parameters gave essentially identical results. The lag between the termination of the infusion and the time for the blood levels to start declining might be an effect of arteriovenous redistribution. The variation in blood concentrations was occasionally quite large. This was probably due to difficulties in achieving a rapid and complete stop of the hydrolysis of the ester in the blood when outside the body. However, the inter-individual variation in estimated PK parameters was small. Furthermore, the intra- and inter-individual variations in blood concentrations and PK parameters of the metabolite (M1) were small. Transformation of the constant rate infusion data to a model for an IV bolus dose showed that the initial phase of the declining blood concentration versus time curve (having $t_{1/2}$ of 1 min) represented more than 80% of the total AUC. A rapid hydrolysis rate *in vitro* in human blood, $t_{1/2}$~5 min. at 37°C, and the coincidence between the termination of the infusion and time to maximum concentration (tmax) for the M1, indicate that the initial phase of clevidipine represented both elimination and distribution. Thus, the terminal phase of the curve reflects distribution of the drug from extravascular tissue into the blood (Figure 5).

Figure 5: Study SAD-0002

Figure 6: Median blood concentration of clevidipine vs. time (n=8)

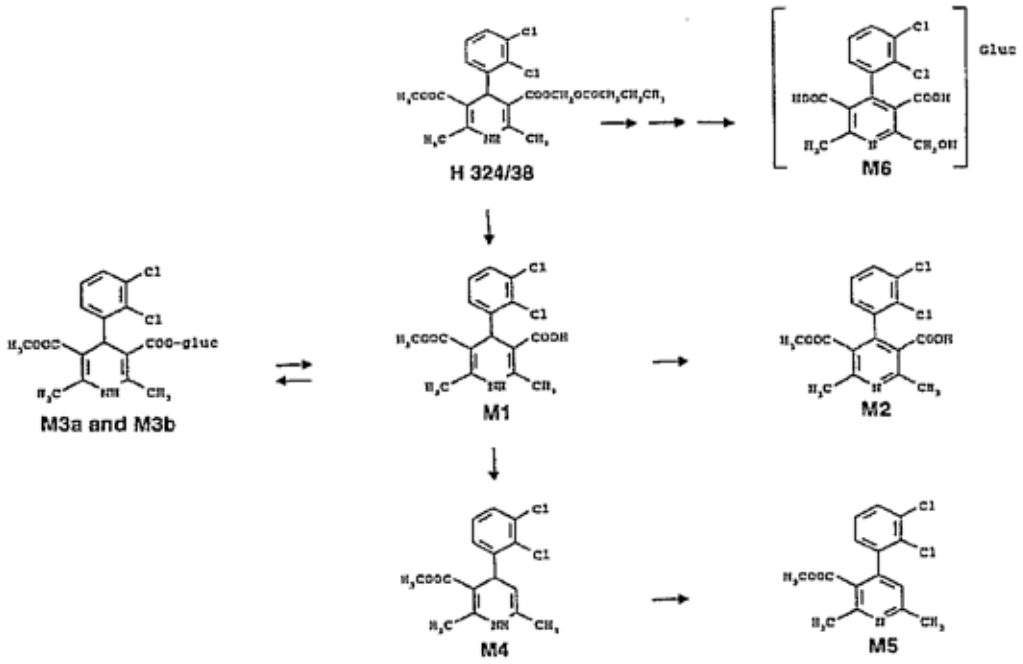


These results imply a rapid achievement of steady state concentration (Css) and a rapid onset of the effect when the infusion is started; with a rapid disappearance of blood drug concentration and effects when the infusion is stopped**.** This is in agreement with the findings in this study where the mean of BP and HR were back to pre-dose values 15 minutes after end of infusion.

The total recovery of radioactivity was 83%; 68% of the total dose was recovered in urine and 15% in faeces, respectively. Recovery of a portion of the administered radioactivity in faeces suggested that biliary elimination was likely to be involved in the excretion of the IV dose. Most of the recovered dose was found within 72 hours. The initial t½ represents >80% of the total AUC is approximately 1 minute, and the terminal t½ is approximately 12 minutes. Results from this study show that clevidipine is a high CL compound rapidly metabolised to the corresponding acid, M1. The high CL value (0.14 L/min/kg) for clevidipine indicates rapid metabolism by hepatic and extrahepatic tissues. These results are consistent with the schematic diagram of the metabolic pathways of clevidipine from pre-clinical studies (Figure 6).

Figure 6:

Figure 9: Metabolic pathways of clevidipine in humans



SAD-0018

The primary objective of the single-dose, open-label, randomised study SAD-0018 was to determine the pharmacokinetic parameters of clevidipine during and after a 20-minute and a 24-hour infusion, and to establish the dose/blood concentration (arterial and venous) – response relationships of clevidipine in 12 healthy volunteers. The two 24-hour-infusion time groups included 4 subjects each receiving final infusion dose of clevidipine 0.91 µg/kg/min (4.32 mg/h) and 3.2 µg/kg/min (16 mg/h) (dose was initially started at 0.5ng/ml and gradually titrated every 10-15mins to the final infusion dose). Another 4 subjects received 7nmol/kg/min (3.2 µg/kg/min or 16 mg/h) ml for 20minutes only (short infusion time group). Frequent arterial and venous blood samples were drawn for estimation of drug blood concentrations before, during and after the end of infusion. A clear difference in arteriovenous blood concentrations was obtained for blood concentrations during ongoing infusion and the arterial concentration was approximately twice as high as the venous blood concentration following constant infusion. After the clevidipine infusion was stopped, the blood concentrations declined rapidly, and after a short time the arterial and venous blood concentrations merged into a common concentration-time profile with very small differences between the arterial and venous clevidipine concentrations.

The CL value obtained from arterial blood concentration was about half of that obtained from venous blood concentration and the volume of distribution (Vd) determined from arterial blood concentration was lower than the corresponding volume determined from venous blood concentration suggesting that the drug is cleared in the tissues before it gets to the venous sampling site. The $t_{1/2}$ determined from venous blood concentration was somewhat longer in the venous blood (probably an effect of blood samples being drawn over a longer period of time). The differences between arterial and venous blood concentrations suggest an extensive and very rapid metabolism of clevidipine in the blood and in the tissues.

The differences between the derived PK parameters following short and long infusion were small. The time for a 50% decrease in the arterial steady state blood level was <1 minute after

both 20 minutes and 24 hours of infusion. The corresponding time for a 90% reduction in Css was 3 and 5 minutes, respectively.

Results from this study show that an arteriovenous blood concentration difference exists during ongoing infusion however differences in the derived PK parameters for both arterial and venous concentrations after a short- and long-term infusion are small. Steady state blood concentrations were achieved within 2 minutes of the initiation of infusion which is reflective of the rapid clearance exhibited by clevidipine.

TMV-CLV-05-01

In study **TMV-CLV-05-01,** blood samples were drawn to determine the concentration of clevidipine and its major metabolite (H152/81) paired with the definitive ECG endpoints. Blood concentrations of clevidipine and its major metabolite were determined using a validated assay method at certain time points; average concentration at Css was calculated and where feasible, the clearance was estimated using the relationship CL =Infusion Rate/Css.

For the therapeutic infusion (3.2 μg/kg/min or 16 mg/h), the mean clevidipine Css remained similar across sequences at approximately 6.5 ng/mL. The calculated mean CL based on the Css during the therapeutic infusion phase was 0.736 L/min/kg.

For the supra-therapeutic infusion phase (12 μg/kg/min or 57.6 mg/h), the mean clevidipine Css were slightly higher in Sequence 2 (21 ng/mL) compared to Sequence 1 (17 ng/mL)**.** Due to insufficient time points at steady state in the supratherapeutic infusion phase, clearance for this phase was not estimated. The combined mean Css of both sequences showed a slightly lower than dose proportional increase between the two doses of therapeutic and supra-therapeutic phases. The increase in mean Css was approximately 2.8-fold for a 3.8-fold increase in clevidipine dose between the therapeutic (3.2 μg/kg/min or 16 mg/h) and supra-therapeutic (12 μg/kg/min or 57.6 mg/h) infusions. However, given the sparse sampling in this protocol, this finding should be considered with caution. The time course of clevidipine followed the predicted pattern with maximal values at the end of the supratherapeutic infusion. Clevidipine blood concentration levels dropped rapidly after the discontinuation of the infusion.

Pharmacokinetics in patients

Pharmacokinetics in patients with essential hypertension

In study **SAD-0004** involving 13 patients with essential hypertension on beta-blocker therapy, a one-compartment model was used to describe the PK profile for clevidipine. This study showed that clevidipine was a high clearance drug with $t_{1/2}$ of approximately 3 minutes**.** An average decrease in MAP of 5%, 10%, and 15% occurred at dose rates of 0.1, 0.2 and 0.6 μg/kg/min, respectively. The corresponding blood concentrations were 1, 4 and 12 nmol/L. The rapid decline in blood concentrations following end of IV infusion seems primarily to be a result of a rapid clearance rather than redistribution as the rate of recovery was rapid regardless of the final infusion rate or the total duration of clevidipine administration.

In study **SAD-0010,** there appeared to be a linear relationship between target dose rate and mean blood concentration of clevidipine. After stopping the infusion, the blood concentrations declined rapidly. A two-compartment model was fitted to the blood concentrations in all patients on the two highest dose rates. It is worth noting that the non-compartmental and compartmental calculations of CL value gave essentially the same results. The mean blood CL values and volume of distribution at steady state (Vdss), calculated for the highest dose rates, were 0.12 L/kg/min and 0.6 L/kg, respectively. These values were

similar to those reported in healthy volunteers (SAD-0002). The blood levels of the enantiomer H190/90 were slightly higher than those of H190/91 due to a marginally higher clearance of the latter compound. The differences in the PK parameters of the enantiomers were small and hence not considered to be of any clinical relevance. The PK results from this study show that clevidipine is a high CL compound and that there is a linear relationship between blood concentrations of clevidipine at steady state and dose rate over the range 0.18 and 5.48 µg/kg/min (0.86 and 26.3 mg/h).

In study **TMC-CLV-06-01** (Table 5) involving 61 patients with mild/ moderate essential hypertension, clevidipine blood concentrations of clevidipine were highly variable throughout the 72-hour infusion period (Figure 7) and decreased in a bi-exponential fashion thereafter following termination of the infusion**.** The concentration time profile was similar across all dose levels of clevidipine. Following IV infusion, there was a less than dose proportional increase in Cmax, Css, and AUC_{0-t} between Cohort 1 (clevidipine 2.0 mg/h) and Cohort 4 (clevidipine 16.0 mg/h) (Table 11)**.** The disproportional behaviour is visibly more pronounced at the lower doses, levelling out for the two highest dose groups. However, given the relatively small number of patients in each dose group, this observation should be interpreted with caution. The mean alpha phase $t_{1/2}$ ranged from 3 to 4 minutes and mean beta phase $t_{1/2}$ ranged from 32 to 37 minutes across dose groups. However, due to the absence of sampling within the first 2 minutes after cessation of clevidipine infusion, the $t_{1/2}$ values reported here are more likely to be the beta and terminal phases, rather than the true alpha and beta phases. The calculated mean clearance value for clevidipine was approximately 30 L/min, and was similar across all dose groups evaluated**.**

Figure 7: Study TMC-CLV-06-01

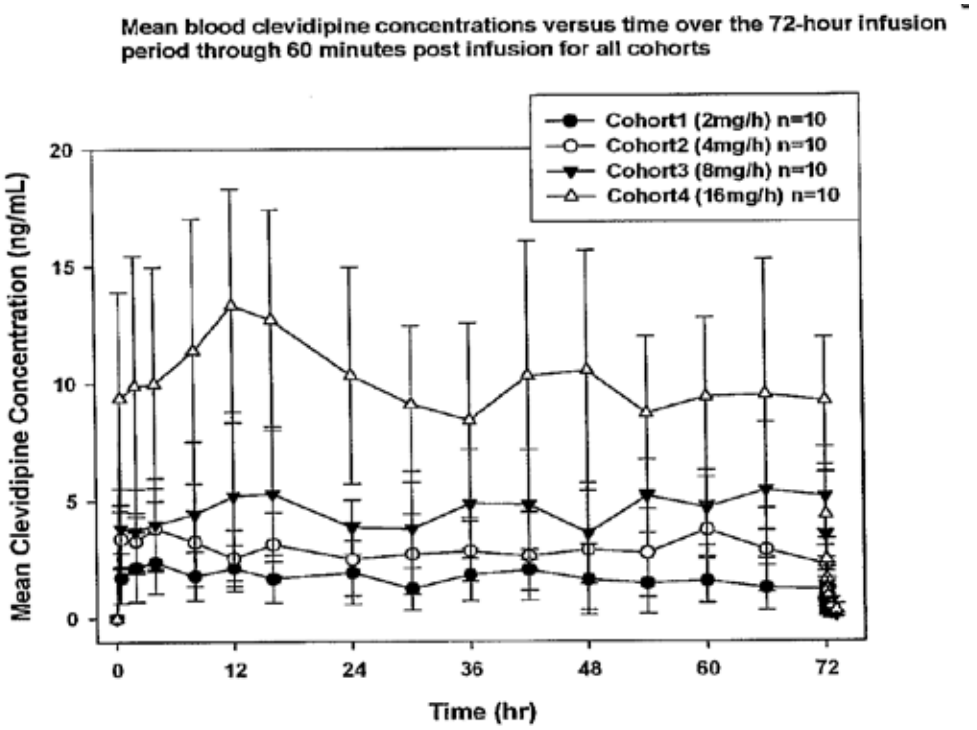


Table 11: Study TMC-CLV-06-01 – Summary of the mean (SD) PK Parameters of Clevidipine

Cohort	**Clevidipine infusion dose (mg/h)**	**N**	**C_{max} (ng/mL)**	**AUC_{0-t} (ng*h/mL)**	**C_{ss} (ng/mL)**	**CL (L/min)**	**$T_{1/2}$ – alpha (min)**	**$T_{1/2}$ – beta (min)**
1	2	10	3.363 (1.348)	122 (56)	1.371 (0.696)	33.2 (21.0)	4.18 (2.59)	NC
2	4	10	5.169 (1.666)	211 (92)	2.995 (1.251)	26.1 (10.9)	3.28 (1.06)	37.0 (29.85)
3	8	10	7.677 (2.370)	327 (1090	5.124 (1.623)	28.5 (9.91)	3.16 (1.4)	32.4 (33.61)
4	16	10	15.762 (4.013)	724 (246)	9.203 (3,371)	33.4 (14.7)	3.34 (0.96)	37.33 (21.66)

Pharmacokinetics in patients with peri-operative hypertension

In study **SAD-0003** (Table 6) involving 91 post-cardiac surgery patients, the PK results demonstrate that clevidipine is a high CL drug with relatively small Vd, initial $t_{1/2}$ of 0.4 minutes and a terminal $t_{1/2}$ of 15 minutes. The initial $t_{1/2}$ of clevidipine is an important feature, as it accounts for more than 99% of the initial concentration or 85% of the total AUC. The terminal tail is less than 1% of the initial concentration. The short $t_{1/2}$ of clevidipine predicts a rapid achievement of steady state blood concentration and a fast onset of effect after start of infusion.

In study **SAD-0005** (Table 8) involving 18 post-cardiac surgery patients**,** blood samples were collected just prior to and after stopping the infusion. During ongoing infusion, the arterial blood concentrations were on average about twice the corresponding venous concentrations. The $t_{1/2}$ of clevidipine in the arterial blood was half of that in the venous blood**.** Following termination of the infusion, the blood concentrations declined rapidly, with the arterial blood concentrations declining faster than the venous concentrations.

In the Phase II study **SAD-0006** (Table 10) involving 17 patients undergoing cardiac surgery, similar blood concentrations of clevidipine in the in-flow and outflow lines of the heart lung-machine suggest that clevidipine is not metabolised or absorbed during the passage through the heart lung machine. The pharmacokinetic parameters were determined pre-bypass (normothermic conditions) and during bypass (hypothermic conditions). During the bypass periods, the body temperature decreased by an average of 4°C. In addition, the hematocrit (Hct) decreased from 0.34 pre-bypass to 0.28 during bypass due to haemodilution. Blood clearance was 0.058L/min/kg during normothermic conditions and 0.030 L/min/kg during hypothermia. The corresponding values of the volume of distribution at steady state were 0.117L/kg and 0.119L/kg, respectively**.** It is likely that the lower clearance during the bypass phase is a consequence of hypothermia rather than haemodilution. This is supported by results from in *vitro* studies in which the rate of clevidipine hydrolysis was reduced at lower temperatures, but not by haemodilution.

Population pharmacokinetics

Population PK and PD analysis of clevidipine was performed using data from Phase II study TMC-CLV-06-01 (patients with mild/ moderate essential hypertension) and Phase III study, TMC-CLV-06-02 (patients with severe hypertension).

The PK data used in the population PK analysis represent all available concentration data collected in TMC CLV 06-01. The primary metabolite (M1) information was not evaluated. The final database used for model building and evaluation consisted of 804 observations from a total of 40 subjects. Data from the PK database were merged with SBP data from all patients enrolled in TMC-CLV-06-01. For the PK/PD database, patients from all dose groups including placebo were included. The final database used for PD model building and evaluation consisted of 2380 SBP observations from a total of 53 subjects. Once a final model was identified, a limited visual predictive check was conducted using data from the external validation database from TMC-CLV-06-02.

Data from study TMV-CLV-06-02 showed that the majority of the observed concentrations fall between the 95% prediction intervals, which is indicative that the model adequately captures the variability in the observed data. Overall the predictive performance of this model was considered adequate.

The evaluation of covariate effects in PK analysis showed an effect of body weight as the most important covariate. Over the range of body weights of 50 to 100 kg, the typical value of clearance changed from 948 to 1594 L/h and further examination of data suggested that height was also potentially important. Therefore, body surface area (BSA) may be a better descriptor of pharmacokinetic variability than weight. In addition, the typical value of clearance increased from 1220 to 1371 L/h for a 70 kg person over the three days of infusion**.** The cause of this effect was not known.

The evaluation of covariate effects in PD analysis showed an effect of age as the most important covariate. Over the age range (20 to 90 years) in this present database, the typical value of SBP increased approximately 13%**.** No other covariates were identified in this evaluation. In general, the PK of clevidipine in subjects with mild to moderate hypertension were well described by a two- compartment open model with first order elimination from the central compartment while the PD of clevidipine as measured by systolic blood pressure were best described using a direct effect linear model. Body weight was found to contribute significantly to inter-individual variability in clearance and the central volume of distribution in this evaluation. There was an indication of time dependent clearance where the clearance increased with time and age was the only covariate to affect SBP. However, the overall effect of covariance is small and should not affect dose of clevidipine planned to be used in the clinical setting since the drug is titrated to the desired haemodynamic effect.

Absorption, Distribution, Metabolism and Elimination profile of clevidipine from results of various studies

Absorption

Since clevidipine is administered via IV infusion, the bioavailability of the drug is 100%. In healthy volunteers (SAD-0001), clevidipine showed a linear relationship between Css and infusion in the range of 1.5 to 48 nmol/kg/min (3.3 to 105.1 mg/h). Similarly, patients with essential hypertension also showed linear relationship between blood concentrations of clevidipine at steady state and dose rate over the range 0.18 and 5.48 μg/kg/min (0.86 and 26.3 mg/h) (SAD-0010) In another study (TMC-CLV-06-01) in which clevidipine was administered as a 72 h infusion, there was a slightly less than dose proportional increase in AUC_{0-t} between clevidipine 2.0 mg/h and clevidipine 16.0 mg/h (~5.9-fold increase in AUC_{0-t}

for an 8-fold increase in dose). This trend is also shown in a decrease in the dose normalised AUC_{0-t} as dose increases. The disproportional behaviour is visibly more pronounced at the lower doses, levelling out for the two highest dose groups. Clevidipine concentrations in the arterial blood were twice that in the venous blood. There was no significant difference in PKs following short-term (20minutes) IV infusion and long-term infusions up to 72 hours.

Distribution and protein binding

The Vd of clevidipine at steady state has been determined in several studies. The mean Vss based on venous blood concentrations ranges from 0.27 to 0.81 L/kg in healthy volunteers, patients with essential hypertension and patients with perioperative hypertension. Corresponding values based on arterial blood concentrations range from 0.08 to 0.22 L/kg. In the dose-ranging study SAD-0003, the Vss was determined to be 0.17 L/kg in arterial blood. Clevidipine is greater than 99.5% bound to proteins in blood at 37oC while its enantiomers H190/90 and H190/91 are bound 99.6% and 99.7%, respectively. Distribution and binding of clevidipine were similar in all populations studied.

Metabolism

Clevidipine butyrate is rapidly metabolised by hydrolysis of the ester linkage, primarily by esterases in the blood and extravascular tissues, making its elimination unlikely to be affected by hepatic or renal dysfunction. The primary metabolite is the carboxylic acid metabolite formed by hydrolysis of the ester group. The carboxylic acid metabolite is inactive and does not show antihypertensive properties. The PK of the primary metabolite H152/81 (M1) differs from that of the parent compound. M1 attains maximum blood levels within minutes after stopping the clevidipine infusion and has a low clearance with a relatively small Vss. It is eliminated at a much slower rate than clevidipine with the initial half-life of 1 hour, the terminal half-life of 9 hours, and clearance of 0.03 L/h/kg. Before being excreted, M1 is further metabolised by glucuronidation or oxidation to the corresponding pyridine derivatives. The main metabolites in urine are M3a and M3b, acyl-glucuronides of M1. In the faeces, the predominant metabolite is M5. The metabolites are formed by 4 metabolic pathways (see Figure 6).

Elimination

Systemic CL has been determined in several studies, by applying compartmental and non-compartmental analysis on individual data or by the population approach. These different calculation methods have yielded similar results. As arterial blood concentrations are approximately twice as high as venous concentrations, the mean blood CL obtained from venous blood samples are about twice as high as those from arterial samples. In healthy volunteers, mean CL values from venous and arterial samples are 0.1–0.2 L/min/kg and 0.07 L/min/kg, respectively (SAD-0018). Corresponding values for patients with perioperative hypertension (after cardiac surgery) were 0.09 and 0.05 L/min/kg, respectively (SAD-0003). During the pre-bypass (normothermia) phase of cardiac surgery, CL was 0.06 L/min/kg and decreased by half during the bypass (hypothermia) phase of the operation to 0.03 L/min/kg (SAD-0006). In all populations studied, CL of clevidipine was highly correlated with the ultrashort $t_{1/2}$ of the drug.

Following termination of an infusion of clevidipine in healthy volunteers, the blood concentration declines in a multiphasic pattern. The initial and terminal $t_{1/2}$ from arterial blood after a final dose rate of 3.2 μg/min/kg (16 mg/h) during short (20 min) and long term (24 hours) infusion (high rate) were 0.6, 15.6 and 0.7, 21.1 minutes, respectively. The corresponding values determined from the venous blood samples were 1.6, 1.6 and 24.1 and 55.8 minutes, respectively (SAD-0018).The venous blood concentrations were followed for a longer period and $t_{1/2}$ was determined with greater precision accounting for differences between $t_{1/2}$ between different pools of blood. However, only a small percentage of the dose is eliminated with the longest $t_{1/2}$.

In patients with essential hypertension exposed to clevidipine for 72 h at dose rates 2.0, 4.0, 8.0, 16.0 mg/h the initial $t_{1/2}$ was 3-4 minutes and terminal $t_{1/2}$ was 32-37 minutes. Longer

terminal $t_{1/2}$ maybe due to an inadequate number of blood samples collected during an α- and β- phases of drug elimination (TMC-CLV-06-01).

In patients with perioperative hypertension, the $t_{1/2}$ calculated from arterial blood concentrations are 0.5-0.6 minutes for the initial phase and 4.1-2.9 minutes for the terminal phase, with approximately 85% of the elimination associated with the initial very rapid phase (SAD-0003). Overall, these data consistently reflect ultrashort α phase $t_{1/2}$ of about 1 minute of clevidipine which accounts for approximately 85-90% of clevidipine elimination.

In a clinical study with radio-labelled clevidipine butyrate, 83% of the drug was excreted in urine and faeces. The major fraction, 63-74% is excreted in the urine, 7-22% in the faeces. More than 90% of the recovered radioactivity is excreted within the first 72 hours of collection.

Clevidipine is not metabolised through hepatic or renal pathways, and its major metabolite, although eliminated via the kidney, has no pharmacologic activity. Hence, lack of evaluation of clevidipine PKs in hepatically or renally impaired patients was not a major limitation of the submission. In addition Phase III studies included data from a large number of hypertensive patients with renal/ hepatic impairments showing no difference in safety profiles from those without such impairments.

Summary of pharmacokinetics

The pharmacokinetics of clevidipine are linearly related to the dose. At dose rates of 0.3 to 3.2 μg/kg/min, the steady state plasma concentrations for clevidipine are 10 to 100 nmol/L (4.57 to 45.7 μg/L), respectively.

Clevidipine concentrations in arterial blood are twofold higher than those in venous blood during continuous infusion. The time to reach steady-state venous blood concentration of clevidipine is less than 5 minutes (2 minutes in arterial blood).

Length of infusion has no effect on the kinetics of clevidipine for infusions of up to 72 hours.

Blood concentrations decline in a multi-phase pattern following termination of the infusion. The alpha phase half-life is approximately 1 minute, and accounts for 85% to 90% of clevidipine elimination. The terminal half-life is approximately 15 minutes.

Rapid metabolism is by esterases in the blood and extravascular tissues to an inactive metabolite which is excreted in the urine and faeces. Elimination is therefore largely independent of liver and renal function.

Pharmacokinetic parameters were similar in normal volunteers, patients with essential hypertension and patients with perioperative hypertension.

Clevidipine and its primary metabolite do not induce or inhibit cytochrome P450 isoenzymes at clinically relevant concentrations. The concentration of clevidipine and its major metabolite inducing/ inhibiting some of the P450 isoforms were at least 10 times higher than the highest clevidipine concentration typically seen in the clinic (16 mg/h at 100 nmol/L). In addition, the magnitude of induction/inhibition was much less than the positive control. Although, clinical interaction studies were not conducted, it appears to be unlikely for clevidipine and it major metabolite to cause cytochrome P450 related drug interactions when used in the dose range required to manage hypertension in man. Clevidipine elimination was not significantly affected by the majority of simultaneously administered drugs or by the deficiency of pseudocholinesterase in some patients.

Anaesthesia does not affect the clearance of clevidipine. Systemic arterial clearance of clevidipine is 5 L/min in healthy volunteers and 4.8 L/min in anaesthetised normothermic

patients. CPB with mild hypothermia and haemodilution reduces the rate of clearance by 50% to approximately 0.03 L/kg/min. However, since clevidipine is titrated to blood pressure lowering effect, any minor differences in clearance in this context would not impact the safety of the dosing regimen due to the individualised patient-specific approach.

Drug Interactions

No *in-vivo* drug interactions studies were conducted.

The objective of study 1264 was to determine the *in vitro* hydrolysis rate of clevidipine in blood in the presence of common anaesthetics and other drugs frequently used during general anaesthesia. The rate of hydrolysis was estimated by measuring the formation rate of the primary metabolite of clevidipine H152/81. The following compounds were tested: sodium thiopental, fentanyl, morphine, isoflurane, diltiazem, propofol, pancuronium bromide and vecuronium bromide. The compounds were added to whole blood, together with clevidipine and the $t_{1/2}$ of clevidipine was determined. Most of the added drugs (fentanyl, morphine, isoflurane, diltiazem, and propofol) did not reduce the formation rate of H152/81 at concentrations 100 times the reported therapeutic concentrations. There was a reduction in the formation rate of H152/81 after addition of vecuronium bromide and pancuronium bromide compared to control values. The maximal reduction in the formation rate was 28% with pancuronium bromide and 26% with vecuronium bromide, respectively**.**

Efficacy

Overview

Efficacy of clevidipine was evaluated in 9 Phase II studies and 6 Phase III studies. Two Phase II studies **(SAD-0004, SAD-0010)** provide safety and efficacy data on a total of 34 patients with mild to moderate hypertension. An additional study **(TMC-CLV-06-01)** in 61 patients with mild to moderate hypertension provides PK, PD and safety data of clevidipine during prolonged (>72hours) continuous infusion. In addition, six Phase II studies in a total of 337 cardiac surgical patients provide dose-response, efficacy and safety data; three studies were conducted postoperatively **(SAD-0003, SAD-0005 and SAD-0006)** and the other three intraoperatively **(SAD-0013, SAD-0017 and TMC-CLV-02-01).**

Two randomized, placebo-controlled Phase III studies **(ESCAPE-1 and 2)** provide efficacy data from a high-risk population of 214 patients treated with clevidipine either prior to or after cardiac surgery. Three Phase III, randomized, open-label, comparator-controlled studies **(ECLIPSE-NTG, -SNP, -NIC)** were performed in the cardiac surgical setting and provided safety data on an additional 752 clevidipine-treated patients.

A Phase III open-label study **(VELOCITY)** of 126 patients (safety population) presenting to the Emergency Department or intensive care unit with severe hypertension provided additional data on clevidipine administered by a controlled dosing titration to desired blood pressure effect, followed by at least 18 hours of continuous clevidipine infusion.

Phase II studies

Phase II studies in essential hypertension

Three studies **(SAD-0004, SAD-0010 and TMC-CLV-06-01)** evaluated the initial efficacy of clevidipine in 95 patients with essential hypertension. These studies excluded patients with congestive heart failure, arrhythmia, recent MI, recent CVA, angina and significant valve disease. One study (TMC-CLV-06-01) included patients with impaired renal and/or hepatic function.

In study **SAD-0004,** clevidipine produced a dose-dependent reduction in MAP in 13 patients with essential hypertension on concomitant treatment with oral beta-blockers; average decrease in MAP of 5%, 10%, and 15% occurred at dose rates of 0.06, 0.2 and 0.6 μg/kg/min corresponding to about 0.3 – 3 mg/h, respectively**.**

In placebo-controlled, Phase II study **SAD-0010** involving 21 patients with moderate essential hypertension, 0.18ug/kg/min was the no-effect dose for clevidipine. Maximal reduction of MAP was about 30%, and the clevidipine dose rate producing half of maximum effect (ED_{50}) was 1.5 μg/kg/min (7.2 mg/h non–weight-based dose); clevidipine dose rates between 0.18 and 5.48 μg/kg/min (corresponding to 0.9 and 27 mg/h) produced dose-dependent reduction in SBP, DBP and MAP with slight increase in HR. Mean values of MAP and recovery times on completing drug administration showed dose-related greater reductions in mean MAP and longer times to recovery with clevidipine dose rates of 0.91, 2.74 and 5.48ug/kg/min compared with placebo and clevidipine 0.18ug/kg/min**.** MAP and HR were back to pre-dose values 15minutes after the infusion of clevidipine was stopped.

In study **TMC-CLV-06-01** (Table 5) involving 61 patients with mild to moderate essential hypertension, no tolerance was developed during continuous clevidipine infusion for 72 hours, with the decrease from baseline in SBP being maintained at relatively constant levels throughout the infusion at all four dose levels (2.0, 4.0, 8.0, and 16.0 mg/h). There was no evidence of rebound hypertension following termination of the clevidipine infusion at all four dose levels and SBP returned rapidly to baseline following cessation of treatment. However, relationship between steady state clevidipine concentrations and pharmacodynamic effect was shallow and a maximum effect was not achieved in this study.

Phase II studies in perioperative hypertension

All the Phase II, perioperative studies enrolled adult cardiac surgery patients, of whom the majority underwent elective coronary revascularisation procedures. Patients with poor left ventricular function, recent myocardial infarction (MI), cerebrovascular accident (CVA), renal or hepatic disease were excluded.

Three of these Phase II studies **(SAD-0003, SAD-0005** and **SAD-0006)** have been discussed in detail in previous sections of this report. Study **SAD-0003** established the therapeutic dose-rate for clevidipine suitable for a clinical setting ranged from 0.18 to 3.19 μg/kg/min (0.9 mg/h to 15.3 mg/h). In study **SAD-0006**, the mean dose rate required to control BP during pre-bypass (2.17 μg/kg/min or 11 mg/h) was higher than that required to control BP during bypass (1.26 μg/kg/min or 6 mg/h), which was most likely due to reduced clevidipine clearance during bypass hypothermia. Results of study **SAD-0005** suggested a dose-dependent vasodilatory effect on coronary vessels with no negative effect on myocardial lactate metabolism.

The other 3 Phase II studies in patients with perioperative hypertension are described below:

The Phase II, double-blind, randomised, double-dummy, parallel group study SAD-0013 (Table 12) compared control of BP between clevidipine and SNP in 30 post-cardiac surgery patients. When the patients had developed a SBP of $\geq$145 mm Hg or a MAP of $\geq$90 mm Hg, they were randomised to 3 hours treatment with intravenous infusion of clevidipine or SNP; the dose of study drug was titrated to reduce MAP to a predefined window of 70-80 mm Hg. Since no empirical data were available, 15 evaluable patients per treatment group in the statistical analysis, with a power of 80% and a significance level of 5%, allowed for a Coefficient of Variation (CV) of 0.9 for the number of dose adjustments.

No statistically significant difference was found between the clevidipine and SNP-treated patients for the primary efficacy variable of number of dose adjustments made in order to

maintain MAP within a predefined window. The mean number of dose adjustments per hour was 4.68 and 3.67 in clevidipine and SNP groups, respectively (clevidipine/ SNP ratio=1.02, 95% CI: -1.35, +3.38, p=0.386). However, these results should be interpreted with caution due to the very wide confidence intervals. There appeared to be a trend of more upward dose adjustments in the clevidipine group compared with the SNP group.

Table 12: Details of Study SAD-0013 Phase II, study in post-cardiac surgery patients

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase II, randomised, double-blind, double-dummy, parallel group study. Duration of Rx= up to 3hrs post-surgery. Follow-up visits at 24hrs post-op and also 4-7days after surgery. 2 centres in the UK	N=30 pts undergoing cardiac surgery (CABG) & developed high BP during post-surgery phase. Age: 44-76yrs, mean=62yrs. Sex: 23M:7F Race: Caucasian=30.	Clevidipine (0.3 mg/mL in 20% lipid emulsion) administered intravenously. The drugs were administered for 3 hours during the post-cardiac surgery phase after surgical (CABG), i.e. after the patients had entered the ICU and under conditions of normalised body temperature (36-37 C), adequate mechanical ventilation (as guided by blood gas analyses) and continuous analgesia (fentanyl) and sedation (propofol). When the patients had developed SBP of $\geq$145 mm Hg or a MAP of $\geq$90 mm Hg, the infusion of clevidipine (active)/SNP(placebo) or SNP(active)/clevidipine(placebo) was titrated to reduce MAP to a predefined window of 70-80 mm Hg and to control MAP within this window.	The number of dose adjustments needed to maintain blood pressure within the window (all dose adjustments made during the 3-hour infusion were registered) and the episodes detected outside the MAP window (as assessed by area under the curve, *AUC)* were counted. Safety.	Safety analysis in 31 pts. 34 AEs reported in 15 of 16 pts in clevidipine group vs 29 AEs by 12 of 15pts in DNP group. All AEs were those commonly reported in this pt population, eg. Atrial fibrillation, post-op complications, increased troponin. SAEs: Clevidipine (clev)=1; SNP=2. No deaths. Discontinuations due to AEs: Clev=1 (hypertension), SNP=1 (hypotension). No difference in bleeding or urine parameters.

The evaluator noted that the concentration of clevidipine used in this study was 0.3 mg/ml and that of SNP was 0.5 mg/ml. The number of dose adjustments made might not be an optimal efficacy variable for the determination of "ease of blood pressure control" since a larger volume, and possibly more dose adjustments, would be required with clevidipine than with SNP for a given dose rate and hence effect. The dose rate or average dose required for blood pressure control may have been a more relevant endpoint in this study.

No statistically significant difference was found for the variable of AUC outside the predefined MAP window, although it appears that clevidipine-treated patients were more likely to have higher MAP, while those treated with SNP were more likely to become hypotensive; hence the total AUC_{MAP} was similar in both treatment groups**.** The AUC outside the predefined HR window was significantly higher in the SNP group than in the clevidipine group.

SAD-0017 was a Phase IIb, double-blind, placebo-controlled, parallel group study in 60 patients undergoing elective-cardiothoracic surgery requiring extracorporeal circulation (patients undergoing cardiac transplantation were excluded), who developed increased blood pressure during any of the surgical phases or in ICU (Table 13). The predefined MAP window was set at different levels during the different parts of the surgical procedure and in the intensive care unit (pre-bypass 70-80mmHg, by-pass 60-70mmHg; post-bypass 70-80mmHg; ICU 70-80mmHg).

Table 13: Details of Study SAD-0017 Phase IIb, placebo-controlled study in cardiac surgery patients

Study design	Subjects demographics	Dosage, duration, route and form of study medication	Endpoints	Safety/AEs
Phase IIb, randomised, double-blind, placebo-controlled, parallel group study. Duration of Rx=12hours. At 2 centres in UK.	N=60 pts patients undergoing cardiac surgery and who developed increased blood pressure during any of the surgical phases or postoperatively Age: 36-83yrs, mean=64yrs. Sex: 46M:14F Race: Caucasian=30.	Clevidipine (0.5 mg/mL in 20% lipid emulsion) administered intravenously or matching placebo. Clevidipine (n=29) doses of 1.92-76.8 ml/h (16-640ug/min) with a starting dose rate of 4.8 ml/h (40ug/min), needed to maintain blood pressure within a predefined blood pressure window was titrated to reduce MAP to a predefined window. Placebo (n=31) pts received 20% Intralipid emulsion. Patients who did not respond to the maximum recommended dose rate range of study drug after 10 minutes of infusion received the addition of commercially available glyceryltrinitrate (GTN). GTN was given according to the manufacturer's instructions (Initial infusion dose rate of 0.2-0.5 ug/kg/min).	Primary- To compare the reduction in mean arterial pressure (MAP) between clevidipine and placebo at 10 minutes after the start of infusion of study drug. Secondary- compare the control of MAP (AUC) between the two Rx groups by relating MAP outside the target MAP window to time between the start of infusion and up to 4 hours. To compare the control of MAP - through the number of interventions* - between the two Rx groups, between the start of infusion and up to 4 hours. -safety: AEs, 12-lead and ambulatory ECG, laboratory parameters. -To assess the health economics of clevidipine in comparison with placebo/GTN.	AE incidence: Clevidipine=72.4%, placebo=74.2%. All AEs were those commonly reported in this pt population, eg. Atrial fibrillation, post-op complications, increased troponin. SAEs: clev=5, placebo=3. No deaths. Discontinuations due to AEs: Clev=2 (MI sand extrasystoles); Placebo=0. No difference in transfusions, infusions/ urine output b/w Rx groups. No other clinically relevant concerns regarding laboratory parameters or vital signs.

The change in MAP from baseline to after 10 minutes of infusion of study drug was analysed using analysis of covariance (ANCOVA), with treatment, centre and history of hypertension (essential hypertension: yes or no) as factors and the baseline value of MAP as a covariate. AUC_{MAP} after start of infusion were log-transformed and analysed using analysis of variance (ANOVA), with treatment, centre, phase in which the infusion was started and history of hypertension as factors. The number of interventions as a means of evaluating control of blood pressure during 0-4 hours after the start of study drug infusion was analysed using ANOVA, with treatment, centre, phase in which the infusion was started and history of hypertension as factors.

The main inclusion criteria were: Two consecutive readings of MAP separated by 5 minutes of > 90 mm Hg during pre-bypass, > 80 mmHg during bypass, > 90 mmHg during post-bypass or > 90 mmHg during ICU and EF > 0.30. The main exclusion criteria were: acute MI within 48 hours prior to the study start; recent cerebrovascular accident (3 months); insulin-dependent diabetes; childbearing potential (female patients must be post-menopausal,

* Interventions defined as: 1. Dose adjustments of study drug and GTN, 2. Administration of volume, 3. Other pharmacological therapy, e.g. -stimulants, diuretics, 4. Mechanical intervention

surgically sterile or using any of the following contraceptive methods: intrauterine device or implantable progesterone device); supine HR >110 beats/minute in conjunction with randomisation MAP assessment; known intolerance to calcium channel blockers; allergy to soya bean oil or egg lecithin (components of the vehicle); pre-existing left bundle branch block or permanent ventricular pacing; infusion of glyceryltrinitrate (GTN) (also abbreviated as NTG) at a rate > 0.7 ug/kg/minute prior to randomisation.

Compared with placebo, patients treated with clevidipine showed statistically significantly greater reduction in MAP from baseline to 10 minutes after start of infusion (-28.2 and -10.5mmHg in clevidipine and placebo groups, respectively; mean diff=-17.7mmHg, 95% CI: -23.1 to -12.3, p<0.001)**.** MAP was better controlled in the clevidipine group than in the placebo group, as judged by significantly smaller AUC_{MAP} versus time outside a predefined MAP window; the total $AUC_{MAP(0-4h)}$ (mmHg x min/h) was statistically significantly smaller in the clevidipine group compared with placebo (clevidipine/ placebo ratio=0.63, 95% CI: 0.53, 0.75, p<0.001), suggesting that clevidipine-treated patients were less likely to have values outside the predefined MAP window**.** However, there was no statistically significant difference between treatment groups in total $AUC_{HR(0-4h)}$, suggesting lack of effect of clevidipine on heart rate**.** The mean number of interventions* to control MAP (0-4h) was also significantly lesser in the clevidipine (32.5) group compared with the placebo (41.3) group (treatment difference=-8.8, 95% CI: -14.7, -2.9, p=0.004); the addition of GTN and its dose adjustments, that is, start and stop of drug infusion, accounted for most of the pharmacological interventions.

TMC-CLV-02-01 was a double blind, prospective, randomised, multicentre, parallel group study comparing clevidipine versus GTN for BP control and preservation of renal function in 100 patients undergoing CABG (Table 14)**.** All patients were to undergo elective CABG on cardiopulmonary bypass (CPB) and scheduled for at least one arterial graft. Women of child-bearing potential must have been postmenopausal, surgically sterile, or using an appropriate contraceptive. The exclusion criteria were similar to those in study SAD-0017 described above.

Clevidipine was administered IV at a minimum dose rate of 0.2 µg/kg/min (non weight-based equivalent calculated for an 80-kg patient was 1 mg/h) after induction of anaesthesia through 12 hours postoperatively. Increases in dose rate to 4.4 µg/kg/min (about 22 mg/h) were permitted for continuous infusion of clevidipine, and up to a maximum infusion of 8 µg/kg/min (about 40 mg/h), provided this dose rate was not infused for longer than 120 minutes.

GTN was administered IV at a minimum dose rate of 0.4 µg/kg/min after induction of anaesthesia until 12 hours postoperatively, with adjustment of dose rate as required to control BP (MAP). Control of BP was assessed from start of study drug until initiation of cardiopulmonary bypass (CPB), by calculation of the AUC value resulting from excursions of MAP above or below pre-defined limits. If the upper limit of the 95% CI was less than 1.50 for the ratio of geometric-means, the results were expected to support a finding of noninferiority.

Postoperative renal dysfunction in each treatment group was assessed in terms of the changes in serum creatinine and calculated creatinine clearance from baseline.

* Interventions defined as: 1. Dose adjustments of study drug and GTN, 2. Administration of volume, 3. Other pharmacological therapy, e.g. -stimulants, diuretics, 4. Mechanical intervention

Urinary N-acetyl glucosaminidase (NAG) was used as marker of renal tubular function.

Clevidipine met pre-defined criteria for noninferiority compared to GTN in controlling BP (ratio of geometric mean= 0.97; 95% CI 0.74-1.29) during the pre-bypass period**.** Clevidipine and GTN were similar with respect to the preservation of glomerular function in patients undergoing CABG on CPB. No significant differences were observed between treatment groups with respect to absolute values or ratios for glomerular function parameters at any time point**.** No statistically significant differences in absolute values or ratios for the renal tubular function parameter of NAG were detected in clevidipine-treated patients compared with GTN-treated patients for almost all time points**.** According to predefined study criteria, the MAP target range was the absolute window of ±5 mmHg associated with the clinician-predetermined target MAP. For both treatment groups, the geometric means of the area under the curve for MAP excursions outside the MAP range normalised per hour (AUC_{MAP-D}) above the predetermined target range were numerically greater than those below the target range; these results suggested that during the pre-bypass period, MAP was assessed above the target range more often than below in both treatment groups and to a comparable extent in each**.** The geometric mean of AUC_{MAP-D} for the aortic cannulation period was larger for patients in the clevidipine group compared with the GTN group, with no statistically significant differences between treatment groups**.** There was no significant difference between treatment groups in the number of study drug adjustments for the pre-bypass period and in the ICU**.** Furthermore, the number of other therapeutic interventions to control MAP (besides study drug) that was recorded per patient was similar in both treatment groups**.** There were no significant differences in perioperative fluid input, output, or the parameters making up these endpoints were found between treatment groups**.**

Table 14: Details of Study TMC-CLV-02-01 Phase II study: clevidipine versus GTN effect on BP control and renal function in cardiac surgery patients

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase IIb, multicentre, randomised, double-blind, parallel group study. Duration of Rx=12hrs. Safety, n=100 (Clev =49, NTG=51). Per protocol=93 (Clev=45, NTG=48). At 3 centres in	N=100 patients undergoing cardiac surgery and who developed increased blood pressure during any of the surgical phases or postoperatively Age: 36-83yrs, mean=64yrs. Sex: 46M:14F Race: Caucasian=30.	Clevidipine (0.5 mg/mL in 20% lipid emulsion) administered intravenously (IV) at a minimum dose rate of 0.2 µg/kg/min (non-weight-based equivalent for an 80-kg patient is 1 mg/h) after induction of anaesthesia through 12 hours postoperatively, with dose adjustment as required to control BP [MAP]. Increase in dose rate to 4.4 µg/kg/min permitted for continuous infusion of clevidipine. The infusion could also be increased to a rate ranging from 4.4 µg/kg/min to 8ug/kg/min, provided this dose rate was not infused for longer than	Primary- compare the control of MAP (by the area under the curve, AUC) between the two Rx groups by relating MAP outside the target MAP window to time between the start of infusion and up to start of CPB (pre-bypass period). Secondary- renal function: Glomerular function (change from baseline to highest value of serum creatinine); tubular function (ratio & difference between the baseline preoperative N-acetylglucoaminidase [NaG normalised for urinary creatinine] and the individual highest NaG in the postoperative period. Urinary & serum sodium, potassium & osmolality.	AE incidence: Clevidipine=63.3%, GTN=58.8%. Hypotension (26.5% vs 15.7%) most common AE in both groups. All AEs were those commonly reported in this pt population, eg. Atrial fibrillation, post-op complications, increased troponin. SAEs: clev=24.5%, GTN=17.6%.1 death in each Rx group & 5 discontinuations due to AEs in each Rx group. Overall, AEs and changes in lab parameters were similar in both groups and compatible with what would be expected in cardiac surgery patients.

USA & 1 centre in New Zealand		120 minutes. The maximum dose rate was 8 µg/kg/min. Glyceryltrinitrate was administered IV at a minimum dose rate of 0.4 µg/kg/min after induction of anaesthesia through 12 hours postoperatively, with adjustment of dose rate as required to control BP (MAP)	Other sec endpoints- number of dose adjustments, treatment interventions, AUC above and below the pre-determined target MAP range; fluid intake and output. -safety: incidence of hypertriglyceridemia, AEs, SAEs, laboratory parameters, ECG and vital signs.	Mean HR was higher in GTN-treated patients compared with clevidipine-treated patients. No pts in either group had hypertriglyceridemia (defined as serum TG levels before normalization of greater than 525 mg/dL) or an AE of hypertriglyceridemia.

The incidence of acute MI and the number of cardiac ischemic episodes requiring therapeutic interventions were similar in both groups**.**

Phase III studies in perioperative hypertension

In the five perioperative Phase III studies, inclusion criteria were broader to increase the risk characteristics of the patients enrolled. Patients having urgent or elective cardiac surgery were included, and there were no restrictions on the presence of renal or hepatic impairment, MI, left ventricular function, or use of inotropic/intra-aortic balloon pump support. The only significant exclusion criterion was recent CVA (within 3 months of screening).

ESCAPE-1 (TMC-CLV-03-01) and ESCAPE-2 (TMC-CLV-03-02)

The ESCAPE studies were Phase III, multicenter, double-blind, placebo-controlled, randomised, parallel-group studies evaluating efficacy of clevidipine in 104 hypertensive patients who were about to undergo cardiac surgery (ESCAPE-1, Table 15) and 110 patients with postoperative hypertension defined as SBP≥140 mmHg within four hours of arrival in a postoperative setting (ESCAPE-2, Table 16).

Table 15: Phase III study: ESCAPE 1 study in pre-operative hypertension

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase III, multicentre, randomised, placebo-controlled, double-blind, parallel group study. Duration of Rx= Minimum of 30 minutes (or until bailout if needed) up to a maximum of one hour (or until induction of anaesthesia, whichever occurred first).	N=105 patients undergoing cardiac surgery and who had pre-operative SBP >160 mmHg after insertion of an arterial line. Age: mean= 62-66yrs. Sex: 73M:32F Race: Caucasian=85, Black=6, Hispanic=10, Others=4	Study drug was administered via a peripheral or central venous infusion using either a syringe pump or a volumetric pump. Clevidipine (n=53) starting infusion rate of 0.4 µg/kg/min (non weight-based equivalent is 2 mg/hr) titrating upward, as tolerated, in doubling increments approximately every 90 seconds up to an infusion rate of 3.2 µg/kg/min (16 mg/hr), in order to achieve the desired blood pressure-lowering effect. Maximum	Primary- incidence of bailout in the clevidipine and placebo treatment groups during the 30-minute time period from initiation of study drug. Secondary- Time to target blood pressure (BP) lowering effect (defined as 15% reduction in SBP from baseline); Change in mean arterial pressure (MAP) from baseline; Incidence of bailout by	AE incidence: Clev vs placebo= 71.7% vs 61.7%. The most commonly occurring TEAEs (pyrexia, atrial fibrillation, nausea) Were those commonly associated with cardiac surgery interventions and the expected perioperative course. SAEs= 24.5% vs 19.6%. 1 death in clevidipine group on first post-op

At 12 centres in USA		clevidipine dose was 8ug/kg/min. Placebo (n=52) consisted of 20% lipid emulsion, the same as the lipid vehicle for clevidipine.	causality. - Safety: AEs, SAEs, vital signs , including change in heart rate (HR) from baseline & laboratory parameters.	day-unrelated. No clinically relevant changes in laboratory parameters; slight increase in HR in clevidipine-treated pts.

The primary objective of the ESCAPE studies was to determine the efficacy of clevidipine versus placebo in treating preoperative (ESCAPE-1) and postoperative (ESCAPE-2) hypertension, by comparing the incidence of bailout in the clevidipine and placebo treatment groups during the 30-minute time period from initiation of study drug. The secondary objectives were to determine the time to target BP-lowering effect (defined as 15% reduction in SBP from baseline), the change in MAP from baseline, the incidence of bailout by causality, and the change in HR from baseline.

Clevidipine was administered in a blinded fashion by IV infusion starting at a rate of 0.4 μg/kg/min (non–weight-based equivalent is 2 mg/h) titrating upward, as tolerated, in doubling increments approximately every 90 seconds up to an infusion rate of 3.2 μg/kg/min (16 mg/h), in order to achieve the desired BP-lowering effect. Up-titration to infusion rates above 3.2 μg/kg/min could be used, guided by the patient's response, by increasing the infusion rate in serial increments of 1.5 μg/kg/min, up to the maximum recommended clevidipine infusion rate of 8.0 μg/kg/min which was not to be exceeded. The infusion was given at minimum 30 minutes (or until bailout if needed) up to a maximum of one hour (or in ESCAPE-1 until induction of anaesthesia, whichever occurred first). The short duration of the assessment period and the option to bail out to alternative antihypertensive therapy preserved the safety of patients randomized to receive placebo. The present study was specifically designed to demonstrate the efficacy of clevidipine as an agent to lower systemic BP to a pre-determined target in hypertensive patients prior to induction of anaesthesia for cardiac surgery.

Table 16: Phase III study: ESCAPE 2 study in post-operative hypertension

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase III, multicentre, randomised, placebo-controlled, double-blind, parallel group study. Duration of Rx= Minimum of 30 minutes after start of infusion, post-operatively, unless bailout occurred, up to a maximum of one hour.	N=110 patients undergoing cardiac surgery and who had post-operative SBP >140 mmHg post-surgery. Age: mean=63yrs, mean=64yrs. Sex: 85M:25F Race: Caucasian=30.	Study drug was administered via a peripheral or central venous infusion using either a syringe pump or a volumetric pump. Clevidipine (n=61) starting infusion rate of 0.4 μg/kg/min (non weight-based equivalent is 2 mg/hr) titrating upward, as tolerated, in doubling increments approximately every 90 seconds up to an infusion rate of 3.2 μg/kg/min (16 mg/hr), in order to achieve the desired blood pressure-lowering effect. Maximum clevidipine	Primary- incidence of bailout in the clevidipine and placebo treatment groups during the 30-minute time period from initiation of study drug. Secondary- Time to target blood pressure (BP) lowering effect (defined as 15% reduction in SBP from baseline); Change in mean arterial pressure (MAP) from baseline; Incidence of bailout by causality. - Safety: AEs, SAEs,	AE incidence: Clev vs placebo= 64% vs 57%. SAEs= 16.4% vs 12.2%. No deaths in study. 2 discontinuations in clevidipine group (due to atrial fibrillation & ventricular tachycardia). No clinically relevant changes in laboratory parameters; slight increase in HR in

At 15 centres in USA		dose was 8ug/kg/min. Placebo (n=49) consisted of 20% lipid emulsion, the same as the lipid vehicle for clevidipine.	vital signs , including change in heart rate (HR) from baseline & laboratory parameters.	clevidipine-treated pts.

The ESCAPE 1 study included patients scheduled for cardiac surgery (including CABG, off-pump coronary artery bypass graft [OPCAB], and minimally invasive direct coronary artery bypass [MIDCAB] surgery and/or valve replacement/ repair procedures) and had a recent history (within six months of randomization) of hypertension requiring treatment with antihypertensive medication(s) or was actively hypertensive upon admission. After insertion of an arterial line, the patient's BP measurement must have met the protocol definition of preoperative hypertension (SBP>160 mmHg). It must have been the investigator's intent to lower the patient's SBP by a minimum of 15% from its baseline value. Exclusion criteria were based primarily on safety considerations; patients were excluded from randomization into the study if they met one or more of the following criteria: Women of child-bearing potential (unless they had a negative pregnancy test), recent cerebrovascular accident (within three months of randomization), known intolerance to calcium channel blockers, allergy to soybean oil or egg lecithin (components of the lipid vehicle), pre-existing left bundle branch block or permanent ventricular pacing, any other disease or condition, which, in the judgment of the investigator would place a patient at undue risk by being enrolled in the trial and participation in another therapeutic drug or therapeutic device trial within 30 days of starting the study.

The inclusion and exclusion criteria for the ESCAPE 2 study were similar, with the exception of the post-operative setting and patients met the following pre-randomisation criteria of: 1) expected to survive beyond 24 hours post-surgical procedure; 2) no surgical complications or conditions, present or anticipated, that precluded them from inclusion in a double-blind, placebo-controlled study; 3) the patient met the protocol definition of postoperative hypertension (SBP $\geq$ 140 mmHg within four hours of arrival in a postoperative setting); and 4) the investigator intended to lower the patient's SBP by a minimum of 15% from its baseline value.

Efficacy endpoints and statistical considerations

The primary efficacy endpoint was the incidence of bailout during the 30-minute efficacy evaluation period, defined as the premature and permanent discontinuation of study drug. Bailout for lack of efficacy was defined as no change or an increase in SBP from pre-treatment baseline, or failure to achieve a nominal reduction in baseline SBP by such time that, in the opinion of the investigator, it became untenable and/or unethical to continue blinded treatment and he/she elected to prematurely and permanently abort study treatment and initiate an alternative open-label IV antihypertensive treatment. Bailout for a safety reason was defined as the occurrence of a treatment-emergent adverse event (TEAE) that, in the opinion of the investigator, necessitated permanent discontinuation of study drug infusion and initiation of an alternative open-label, IV antihypertensive treatment. Bailout due to treatment failure was defined as failure to achieve a minimum reduction of 15% in pre-study drug baseline SBP prior to the completion of the 30 minute period from study drug initiation. Secondary efficacy endpoints included time to target BP lowering effect, change in MAP from baseline, and causality for bailout.

The efficacy analysis was based on the modified intent-to-treat (mITT) population, which consisted of all randomized patients who met the post-randomization inclusion criteria

immediately prior to the initiation of blinded study drug infusion. Missing data points for the bailout evaluation were imputed to be YES for the clevidipine group and NO for the placebo group in order to accommodate a worst-case scenario. The proportion of patients who bailed out were summarized according to treatment group and compared using the Chi-square test. Continuous variables were analysed using an analysis of covariance (ANCOVA) model for absolute change from baseline and an ANOVA model for percentage change from baseline. The time-to-event variable (time to achievement of target SBP reduction) was analysed using the log-rank test and presented by Kaplan-Meier survival curves.

A success rate (no bailout) for the clevidipine group was assumed to be 40% compared with 12% for the placebo group. Fifty patients per treatment group would have at least 85% power to demonstrate this difference between the two groups at a 2-sided significance level of 0.05.

Baseline demographics and disease characteristics

In the ESCAPE 1 study, treatment groups were similar with respect to most demographic and baseline characteristics**.** However, patients randomized to the clevidipine group were older (those >65 years were 63% and 35% in clevidipine and placebo groups, respectively) and had more frequently experienced prior myocardial infarction compared to those randomized to placebo; patients randomized to placebo had a higher incidence of family history of coronary artery disease compared to those randomized to clevidipine**.** The majority of patients had isolated CABG surgery (clevidipine vs placebo: 79% vs 85%) with no significant differences between treatment groups**.**

In the ESCAPE 2 study, treatment groups were similar with respect to most demographic and baseline characteristics However, there were a greater number of patients 65 years old or older and a higher incidence of congestive heart failure in patients randomized to the clevidipine group, while patients randomized to placebo had a higher incidence of angina pectoris**.** The majority of procedures performed were isolated primary CABG surgeries. Valve replacement or repair was performed more frequently in clevidipine-treated patients**.**

Efficacy results

Results of ESCAPE 1 study

Clevidipine was more effective than placebo in treating preoperative hypertension when titrated to effect in this high-risk cardiac surgical population. Efficacy was demonstrated by a statistically significantly higher rate of treatment success (absence of bailout) in the clevidipine group when compared with the placebo group (92.5% vs 17.3%, p<0.0001).

BP was lowered to some degree in all clevidipine treated patients. Only four patients treated with clevidipine required bailout, the reason for which was treatment failure in all cases. Of the 43 patients treated with placebo who required bailout, the reason given was either treatment failure or lack of efficacy (Table 17).

Table 17: Treatment Success vs Bailout and Reason for Bailout (mITT populations) in ESCAPE 1

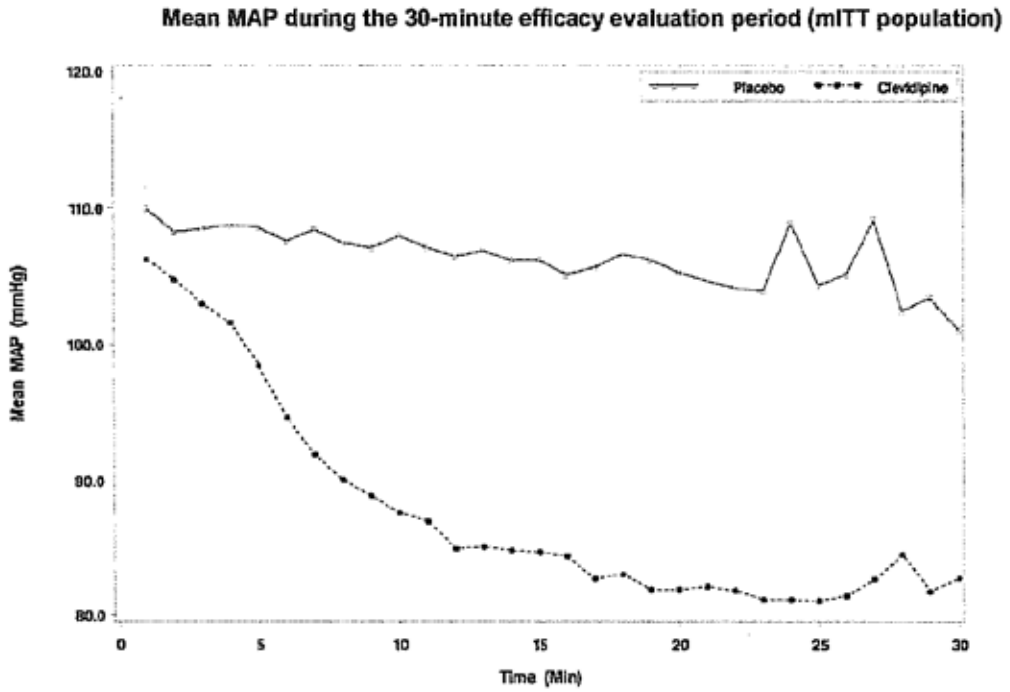
Parameter		Randomised Treatment		
		Clevidipine N=53, n (%)	**Placebo N=52, n (%)**	**p value**
Treatment success		49 (92.5)	9 (17.3)	<0.0001
Bailout (all-cause)		4 (7.5)	43 (82.7)	<0.0001
Reason for bailout	Lack of efficacy	0 (0.0)	18 (41.9)	
	Safety reason	0 (0.0)	0 (0.0)	
	Treatment failure	4 (100.0)	25 (58.1)	

Clevidipine demonstrated a rapid onset of effect; the median time to achievement of a >15% reduction in SBP from baseline in patients treated with clevidipine was 6.0 minutes. This variable was not estimable in the placebo group because so few patients treated with placebo achieved the target SBP.

The majority of patients treated with clevidipine achieved treatment success at a dose of 3.2 µg/kg/min (16 mg/hr) or less. There was a greater decrease in the MAP relative to baseline in clevidipine-treated patients compared to those treated with placebo throughout the 30-minute efficacy evaluation period (Figure 8)**.**

The efficacy of clevidipine over placebo in this setting of postoperative hypertension was not affected by age, sex, race, history of hypertension, CAD, diabetes, dyslipidaemia, smoking or using of other antihypertensive medication during first 10 minutes of infusion**.**

Figure 8: Study TMC-CLV-03-01-ESCAPE-01



Results of ESCAPE 2 study

Clevidipine demonstrated a statistically significantly lower rate of bailout than placebo (p <0.0001). Treatment success (absence of bailout) was reported in 56 out of 61 (91.8%) patients receiving clevidipine as compared to 10 out of 49 (20.4%) patients receiving placebo.

None of the patients in the clevidipine group and 37 patients in the placebo group had bailout for lack of efficacy (Table 18). Two patients in the clevidipine group and two patients in the placebo group had treatment failure as the reason for bailout. No patients in the placebo group had bailout for safety reasons. Three patients in the clevidipine group had bailout for safety reasons (one due to atrial fibrillation, and two due to a decrease in BP [SBP of about 100 mmHg]).

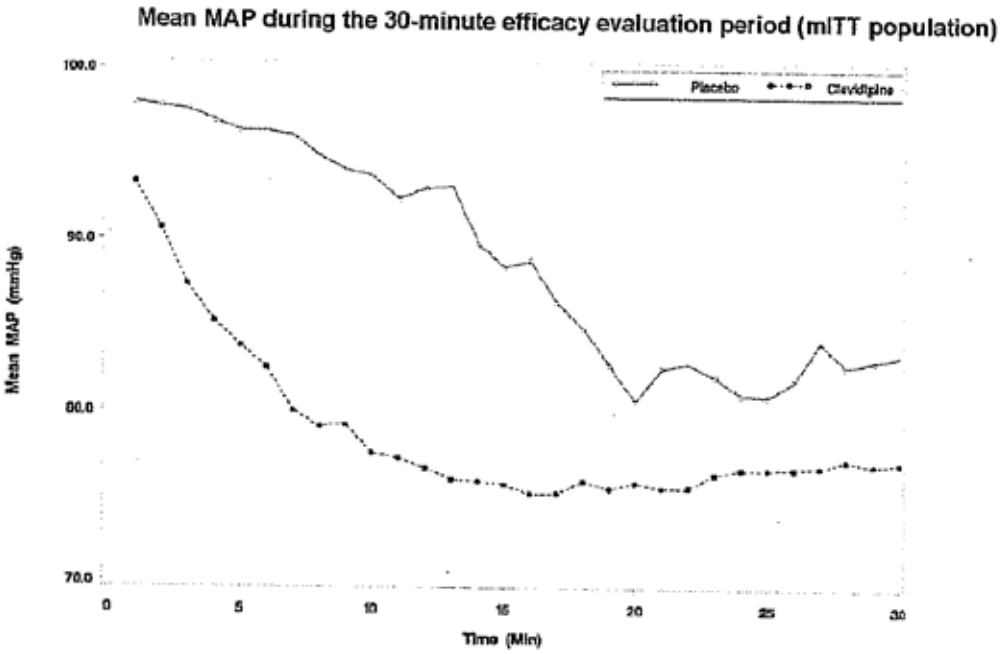
Table 18: Treatment Success vs Bailout and Reason for Bailout (mITT populations) in ESCAPE 2

Parameter		Randomised Treatment		
		Clevidipine N=61, n (%)	**Placebo N=49, n (%)**	**p value**
Treatment success		56 (91.8)	10 (20.4)	<0.0001
Bailout (all-cause)		5 (8.2)	39 (79.6)	<0.0001
Reason for bailout	Lack of efficacy	0 (0.0)	37 (94.9)	
	Safety reason	3 (60.0)	0 (0.0)	
	Treatment failure	2 (40.0)	2 (5.1)	

The target BP (15% reduction in SBP) was achieved at a median of 5.3 minutes in the clevidipine-treated group. This variable was not estimable in the placebo group because an insufficient number of patients treated with placebo achieved the target SBP. The mean

percent change in MAP from baseline to the lowest MAP was -28.9% in clevidipine-treated patients compared with -8.7% in placebo-treated patients (Figure 9).

Figure 9: Study TMC-CLV-03-02-ESCAPE-02



The efficacy of clevidipine over placebo in this setting of postoperative hypertension was not affected by age, sex, race, history of hypertension, CAD, diabetes, dyslipidaemia, smoking or using of other antihypertensive medication during first 10 minutes of infusion**.**

ECLIPSE studies

The ECLIPSE phase 3 programme was conducted as three prospective, parallel group, open-label, randomised (1:1) comparative studies. Patients were randomised to blood pressure management using clevidipine or GTN (ECLIPSE-NTG; TMC-CLV-03-03) (Table 19), or SNP (ECLIPSE-SNP; TMC-CLV-03-04) (Table 20), or nicardipine (NIC) [ECLIPSE-NIC; TMC-CLV-03-05] (Table 21).

The primary objective of the ECLIPSE studies was to establish the safety of clevidipine in the treatment of perioperative hypertension (ECLIPSE-NTG, ECLIPSE-SNP), and postoperative hypertension (ECLIPSE-NIC) by comparing the incidences of death, stroke, MI and renal dysfunction in the clevidipine and comparator treatment groups from the initiation of study drug infusion through postoperative Day 30. A key secondary objective was to examine the efficacy of study drug by evaluating BP control within protocol prespecified SBP ranges as determined by AUC analysis and by the use of alternative antihypertensive agents. This analysis was planned as descriptive, without definitive hypothesis testing.

In ECLIPSE-NTG, 546 patients were treated with study drug (268 clevidipine and 278 GTN), in ECLIPSE-SNP, 579 patients were treated with study drug (296 clevidipine and 283 SNP), and in ECLIPSE-NIC, 381 patients were treated with study drug (188 clevidipine and 193 NIC). The patient population in all ECLIPSE studies consisted of patients undergoing CABG, off-pump coronary artery bypass (OPCAB), or minimally invasive direct coronary artery bypass (MIDCAB) surgery and/or valve replacement/repair procedures, and requiring treatment for hypertension perioperatively (ECLIPSE-NTG, -SNP) or postoperatively (ECLIPSE-NIC). Exclusion criteria were based primarily on safety considerations. Patients were excluded from randomization into the study if they met one or more of the following

criteria: Women of child-bearing potential (unless they had a negative pregnancy test), recent cerebrovascular accident (within three months of randomization), known intolerance to calcium channel blockers, allergy to soybean oil or egg lecithin (components of the lipid vehicle), pre-existing left bundle branch block or permanent ventricular pacing, any other disease or condition, which, in the judgment of the investigator would place a patient at undue risk by being enrolled in the trial and participation in another therapeutic drug or therapeutic device trial within 30 days of starting the study.

Table 19: Phase III study: ECLIPSE-NTG; TMC-CLV-03-03 in post-operative hypertension

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase III, multicentre, prospective, randomised, open-label, parallel group study. Duration of Rx= From time of arterial line insertion during perioperative hypertension till required or till discharge from ICU. Follow-up done till 30 days after discharge from ICU. At 28 centres in USA	N=546 patients undergoing cardiac surgery and who had Age: mean=64yrs. Sex: 421M:125F Race: Caucasian=457, Black=31, Asian=22, Hispanic=30, Others=6.	Study drug was administered via a peripheral or central venous infusion using either a syringe pump or a volumetric pump. Clevidipine (n=268) starting infusion rate of 0.4 µg/kg/min (non weight-based equivalent is 2 mg/hr) titrating upward, as tolerated, in doubling increments approximately every 90 seconds up to an infusion rate of 3.2 µg/kg/min (16 mg/hr. Infusion rates above 3.2 µg/kg/min were permitted in serial increments of 1.5 µg/kg/min, guided by the patient's response. Infusion rates between 4.4 and 8.0 µg/kg/min were to be administered for no more than 2 hours. Maximum clevidipine dose was 8ug/kg/min. GTN (n=278).	Primary- comparing incidences of death, stroke, myocardial infarction (MI) and renal dysfunction in the clevidipine and glyceryltrinitrate (GTN) treatment groups from the initiation of study drug infusion through postoperative Day 30. Secondary- efficacy- area under the curve (AUC) analysis capturing the magnitude and duration of SBP excursions outside predefined ranges (65-135 mmHg intraoperatively and 75-145 mmHg preoperatively and postoperatively); use of alternative IV antihypertensive agents for blood pressure control. Safety: changes in heart rate (HR); incidence of reflex tachycardia; incidence of supraventricular tachy-arrhythmias (SVT) including atrial fibrillation and flutter (AF);incidence of hypovolaemia and total volume of fluids administered; incidence of serious and non-serious AEs; clinical laboratory parameters including haematology, biochemistry, and lipids.	AE incidence: Clev vs GTN= 99.6% vs 100%; incision site complications, atelectasis, atrial fibrillation and pleural effusion most common in both Rx groups. SAEs= 16% vs 18.3%. Deaths: Clev vs GTN= 7 vs 9, all unrelated to study drug. Discontinuations due to AEs: Clev=4.9% vs GTN=1.4%. Median % change from baseline in HR was 31.4% vs 32.1%. SVT (including AF)= 36.6% vs 34.9%. Reflex tachycardia= 0.7% vs 0.4%. No clinically relevant changes in laboratory parameters; slight increase in HR in clevidipine-treated pts.

Clevidipine was administered IV at an initial infusion rate of 0.4 µg/kg/min (non–weight-based equivalent is 2 mg/h) and titrated to BP-lowering effect. The study drug could be titrated in doubling increments approximately every 90 seconds up to 3.2 µg/kg/min (16 mg/h). Infusion rates above 3.2 µg/kg/min were permitted in serial increments of 1.5 µg/kg/min, guided by the patient's haemodynamic response. Clevidipine was titrated to

achieve a patient-specific reduction in BP according to investigator' judgement and was pre-defined.

None of the active comparators is approved for use in a rapid up-titration scheme. Nor can any of them be diluted to allow both rapid up-titration while complying with each drug's approved dose regimen and acceptable standards of care. Due to the lipid emulsion, a double-blind study design would have involved the anticipated administration of Intralipid as the placebo for clevidipine, along with administration of active comparator drug and its placebo. This approach would likely mask any adverse effects due to the lipid emulsion vehicle in the clevidipine arm. Also, because compatibility with other drugs was not known, no other medication was allowed to be mixed with clevidipine before or during administration via the same dedicated IV line. The administration of either clevidipine and placebo comparator, or a placebo for clevidipine and active comparator, would have needed two separate IV lines for each patient. These requirements would have unduly complicated the surgical procedures during the perioperative setting for high-risk patients undergoing cardiac surgery, and potentially could have jeopardised patient safety. Therefore, an open-label design was deemed the most practical and feasible method for conducting the ECLIPSE studies for the treatment of perioperative hypertension in high-risk patients undergoing cardiac surgery.

Table 20: Phase III study: ECLIPSE-SNP; TMC-CLV-03-04 in pre-operative hypertension

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase III, multicentre, prospective, randomised, open-label, parallel group study. Duration of Rx= From time of arterial line insertion during perioperative hypertension till required or till discharge from ICU. Follow-up done till 30 days after discharge from ICU. At 35 centres in the USA	N=579 patients undergoing cardiac surgery and who had Age: mean=64yrs. Sex: 421M:125F Race: Caucasian=481, Black=59, Asian=17, Hispanic=17, Others=4	Study drug was administered via a peripheral or central venous infusion using either a syringe pump or a volumetric pump. Clevidipine (n=296) starting infusion rate of 0.4 µg/kg/min (non weight-based equivalent is 2 mg/hr) titrating upward, as tolerated, in doubling increments approximately every 90 seconds up to an infusion rate of 3.2 µg/kg/min (16 mg/hr. Infusion rates above 3.2 µg/kg/min were permitted in serial increments of 1.5 µg/kg/min, guided by the patient's response. Infusion rates between 4.4 and 8.0 µg/kg/min were to be administered for no more than 2 hours. Maximum clevidipine dose was 8ug/kg/min.	Primary- comparing incidences of death, stroke, myocardial infarction (MI) and renal dysfunction in the clevidipine and glyceryltrinitrate (GTN) treatment groups from the initiation of study drug infusion through postoperative Day 30. Secondary- efficacy- area under the curve (AUC) analysis capturing the magnitude and duration of SBP excursions outside predefined ranges (65-135 mmHg intraoperatively and 75-145 mmHg preoperatively and postoperatively); use of alternative IV antihypertensive agents for blood pressure control. Safety: changes in heart rate (HR); incidence of reflex tachycardia; incidence of supraventricular tachy-arrhythmias (SVT) including atrial fibrillation and flutter (AF);incidence of hypovolaemia and total volume of fluids	AE incidence: 100% in each Rx group; most common TEAEs were atelectasis and incision site complications in both Rx groups, followed by AF in the clevidipine-treated patients and anaemia in the SNP-treated patients. SAEs: Clev vs SNP=19.3% vs 23.3%. Deaths: Clev vs GTN= 7 vs 9, all unrelated to study drug. Discontinuations due to AEs: Clev=2.4% vs SNP=2%. Median % change from baseline in HR was 26.9% vs 30.3%. SVT (including AF)=41.9% vs 40.6% Reflex tachycardia=1.4% in each group.

		SNP(n=283).	administered; incidence of serious and non-serious AEs; clinical laboratory parameters including haematology, biochemistry, and lipids.	Hypovolaemia= 0.7% vs 0.4%. No clinically relevant changes in laboratory parameters.

Efficacy endpoints and statistical considerations

The primary endpoint of all three ECLIPSE studies was a comparison of the incidences of death, stroke, MI, and renal dysfunction that occurred from the initiation of study drug infusion through postoperative Day 30 in each treatment group, as adjudicated by an independent, blinded Clinical Events Committee (CEC). The investigators recorded the incidence of these events using the protocol-specified definitions, as follows:

-Death: all-cause mortality, classified as cardiovascular or non-cardiovascular;

-Stroke: defined as hemorrhagic or ischemic stroke, as diagnosed by a neurologist utilizing clinical signs and/or radiological means of investigation, including arteriography, computed tomography (CT) or magnetic resonance imaging (MRI) scans and/or carotid ultrasound;

-Myocardial infarction: as defined by symptomatic presentation, cardiac enzyme determinations (such as CK-MB or CK in the absence of CK-MB determination or troponin, as per institutional practice) and/or new ECG changes;

-Renal dysfunction: defined as a postoperative (post-randomization), verified (ie, the persistence of serum creatinine elevation 24 h following the initial acute serum creatinine elevation) serum creatinine level of >2.0 mg/dL (177 μmol/L) and an increase of verified serum creatinine level of >0.7 mg/dL (62 μmol/L) from pre-randomization to maximum post-randomization values and/ or the need for haemodialysis, venovenous or arterial venous haemofiltration, or peritoneal dialysis after surgery.

Efficacy was evaluated as a secondary efficacy endpoint in all 3 ECLIPSE studies. Pre-specified ranges (65-135 mmHg intraoperatively and 75-145 mmHg preoperatively and postoperatively) were used to determine the magnitude and duration of BP excursions outside the upper and lower limits of these; use of alternative IV antihypertensive agents for blood pressure control was the other efficacy endpoint. Blood pressure was recorded for 24 hours following study drug initiation. Preoperatively, BP measurements were taken every 15 minutes; intraoperatively BP was recorded every 5 minutes; postoperatively BP was measured every 15 minutes for 4 hours, and then once every hour through 24 hours. These data were used to calculate the AUC as defined above. Due to the unblinded nature of the ECLIPSE studies, post-hoc analyses were performed to assess the potential for bias in the evaluation of the efficacy results demonstrated by the analysis of AUC. Each of the following potentially susceptible biases was considered: (1) subject selection/enrolment, (2) BP measurement, (3) patients' knowledge of treatment received, and (4) disparity in use of concomitant medications (specifically for any alternative IV antihypertensive agents for BP control).

Other secondary endpoints in the ECLIPSE studies were safety-related (AEs, SAEs, laboratory parameters) and also included analysis of change in HR and incidence of reflex tachycardia, SVT (including AF) and hypovolaemia (and fluid input/ output).

There was no formal sample size and/or study power calculation; the total sample size was chosen based on clinical experience and in agreement with the FDA. No formal statistical hypothesis testing was performed in the ECLIPSE studies; 95% confidence intervals and p-values were provided to demonstrate the strength of the findings.

The ECLIPSE study methods were chosen to minimise the potential for bias. Patients were randomised through a centralised randomisation procedure utilising an interactive voice response (IVR) system. The investigators had no knowledge of the next treatment assignment and the decision to enrol patients in the ECLIPSE studies was independent of treatment allocation. The SBP values obtained by means of an arterial line were objective measurements, minimizing the potential for bias related to efficacy measurement. Prespecified BP ranges used to derive AUC were prospectively defined in the protocol, and were defined to be identical for all treatment groups.

Baseline demographics and disease characteristics

In ECLIPSE-NTG, clevidipine and GTN treatment groups were similar with respect to demographic characteristics and baseline SBP and DBP**.** Medical history was similar in both treatment groups, although the incidence of prior CABG in the GTN group was more than twice that in the clevidipine group (clevidipine vs GTN: 3.7% vs 8.6%). Most patients had a history of hypertension (83.6% vs 86.3%) and the majority (approximately 83% in each treatment group) had taken at least one ACE inhibitor, beta-blocker or calcium channel blocker within two weeks of surgery. The most common medication used in both treatment groups was beta-blockers, used by 64.2% of clevidipine-treated patients and 69.1% of GTN-treated patients; prior calcium channel blockers were used in 19.4% of clevidipine-treated patients and 21.6% of GTN-treated patients. During the study, most patients in both treatment groups had a single procedure, with CABG being the most frequently performed and the duration and complexity of the surgical procedures were similar in both treatment groups.

Table 21: Phase III study: ECLIPSE-NIC; TMC-CLV-03-05 in post-operative hypertension

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase III, multicentre, randomised, placebo-controlled, double-blind, parallel group study. Duration of Rx= Minimum of 30 minutes after start of infusion, post-operatively, unless bailout occurred, up to a maximum of one hour. At 28 centres in USA	N=381 patients undergoing cardiac surgery and who had post-operative SBP >140 mmHg post-surgery. Age: mean=66yrs, Sex: 264M:117F Race: Caucasian=304, Black=50, Hispanic=23, Asian=1, Others=3.	Study drug was administered via a peripheral or central venous infusion using either a syringe pump or a volumetric pump. Clevidipine (n=188) starting infusion rate of 0.4 µg/kg/min (non weight-based equivalent is 2 mg/hr) titrating upward, as tolerated, in doubling increments approximately every 90 seconds up to an infusion rate of 3.2µg/kg/min (16 mg/hr), in order to achieve the desired blood pressure-lowering effect. Maximum clevidipine dose was 8ug/kg/min. Nicardipine (n=193).	Primary- incidence of bailout in the clevidipine and placebo treatment groups during the 30-minute time period from initiation of study drug. Secondary- Time to target blood pressure (BP) lowering effect (defined as 15% reduction in SBP from baseline); Change in mean arterial pressure (MAP) from baseline; Incidence of bailout by causality. Safety: AEs, SAEs, vital signs, including change in heart rate (HR) from baseline & laboratory parameters.	AE incidence: Clev vs NIC= 99.5% vs 100%. most common TEAEs in both treatment groups were incision site complication, atelectasis, AF, and nausea. SAEs= 17.6 vs 17.6%. Deaths= 8 vs 6. Discontinuations due to AEs= 6.9% vs 5.7% Median % change from baseline in HR was 27.4% vs 30.7%. SVT (including AF)=41.5% vs 37.8% Reflex tachycardia=0.5% vs 0%. Hypovolaemia= 0% vs 1.6%. No other clinically relevant changes in laboratory parameters.

In ECLIPSE-SNP, clevidipine and SNP treatment groups were similar with respect to demographic characteristics, baseline SBP and DBP**,** medical history with most patients having a history of hypertension and CABG was most common surgery with similar duration and complexity of surgical procedures in both treatment groups. The clevidipine and SNP groups were similar with regard to the type of antihypertensive medication used; the most common types of medication used in both treatment groups were beta-blockers (64.9% and 66.8% of clevidipine-treated and SNP-treated patients, respectively) and calcium channel blockers (23% and 21.2%, respectively). Concomitant medication use was also similar between treatment groups with antihypertensives, sedatives, diuretics most common in both groups.

The baseline demographics, disease characteristics and concomitant medications were similar in the clevidipine and nicardipine groups in **ECLIPSE-NIC.**

Efficacy results

ECLIPSE- NTG

The median total area under the curve for SBP excursions below predefined SBP range normalised per hour (AUC_{SBP-D}) was statistically significantly lower in the clevidipine-treated patients than that observed in the GTN-treated patients (p=0.0006). In addition, the median AUC_{SBP-D} above the target range was statistically significantly lower in the clevidipine-treated patients compared to GTN-treated patients (p=0.0002). The median value for AUC_{SBP-D} below the target range was zero in both treatment groups. Individual AUC_{SBP-D} values were ranked, regardless of treatment group, in order to define patient quartiles and the prevalence of patients from each treatment group within each quartile was compared. A statistically significantly (p=0.0019) larger number of GTN-treated patients were found in the upper two quartiles whereas the reverse was observed for clevidipine-treated patients**.** The percentage of patients who received an alternative antihypertensive agent during the hemodynamic assessment period was similar in both treatment groups (57.8% for clevidipine and 56.8% for glyceryltrinitrate). The pattern of use of alternative antihypertensive drugs was similar in both treatment groups with the exception of nitroferricyanide derivatives (SNP), which were used more frequently in GTN-treated patients (10.8%) compared to those treated with clevidipine (1.1%)**.**The most common reason for use of alternative antihypertensive agents in both treatment groups was for the treatment of hypertension**.**

ECLIPSE-SNP

The majority of clevidipine-treated patients were managed with a maximum weight adjusted infusion rate of $\leq$3.13 μg/kg/min (non weight adjusted, 13.33 mg/h).Clevidipine provided significantly better BP control within the first 24 hours compared to SNP (Total AUC_{SBP-D}: 4.37 versus 10.5 mmHg x min/h, respectively, p=0.0027). The distribution of the AUC_{SBP-D} below target range was different for clevidipine than SNP (p=0.0006), consistent with the fact that SNP-treated patients experienced SBP below the target range (overshoot) more frequently than clevidipine-treated patients**.**

The requirement for additional antihypertensive agents was lower in the clevidipine group compared to SNP (42.8% versus 52.8%, respectively). In the clevidipine group, the most frequently used classes of antihypertensive agents were selective beta-blocking agents (30%), organic nitrates (10.1%), ACE inhibitors (5.1%), and nitroferricyanide derivatives (3.4%). In the SNP group, the most frequently used classes of antihypertensive agents were selective β-blocking agents (31%), organic nitrates (16.9%), ACE inhibitors (11.6%), and dihydropyridine derivatives (6%). The most frequently reported reason for using an alternative antihypertensive agent was for the treatment of hypertension, which was more

frequent in the SNP-treated patients than the clevidipine-treated patients (SNP, 55.3%; clevidipine 45.1%, respectively**.**

ECLIPSE-NIC

The majority of clevidipine-treated patients were managed with a maximum weight-adjusted infusion rate of ≤3.20 ug/kg/min (non weight-adjusted, 14.86 mg/h).

Analysis of AUC_{SBP-D} data demonstrated that there were no statistically significant differences between clevidipine and NIC-treated patients with regard to the median duration of AUC, total hourly normalized area of actual SBP outside target range (AUC_{SBP-D}), or AUC_{SBP-D} above or below the target range. The prevalence of patients by quartiles of total AUC_{SBP-D} was also similar between treatment groups**.**

The percentage of patients who received an alternative or additional non-study IV antihypertensive agent for the treatment of hypertension during the hemodynamic assessment period (from the initiation of study drug infusion through the last recorded SBP measurement) was similar in both treatment groups (40.4% for clevidipine and 39.5% for NIC). The pattern of use of alternative antihypertensive drugs was similar in both treatment groups. The most common reason for use of alternative antihypertensive agents in both treatment groups was for the treatment of hypertension.

Phase III study in severe hypertension

TMC-CLV-06-02 (VELOCITY) was a prospective, open-label, single-group study in 126 patients with severe hypertension (SBP>180mmHg and DBP>115mmHg on at least 2 successive occasions, 15 minutes apart) and were either in the ICU, critical care unit (CCU) or Emergency Department (ED) (Table 22). The main exclusion criteria were:

- Expectation that the patient would not tolerate IV antihypertensive therapy for a minimum of 18 hours;
- Known or suspected aortic dissection;
- Administration of an agent for the treatment of hypertension within the previous 2 hours of clevidipine administration;
- Positive pregnancy test;
- Intolerance to calcium channel blockers;
- Allergy to soybean oil or egg lecithin;
- Known liver failure or cirrhosis;
- Severe hypertension known to be precipitated by use of, or withdrawal from, alcohol or illicit drugs, or intentional overdose of illicit or prescription drugs and participation in other clinical research studies involving the evaluation of other investigational drugs or devices within 30 days of enrolment.

Table 22: Phase III study: VELOCITY in severe hypertension

Study design	**Subjects demographics**	**Dosage, duration, route and form of study medication**	**Endpoints**	**Safety/AEs**
Phase III, multicentre, prospective, open-label,	N=126 patients with severe hypertension, defined as SBP >180 mmHg and/or DBP >115	Clevidipine (n=) was initiated via peripheral venous or by central venous infusion at a rate of 2.0 mg/h and maintained for the first 3 minutes. If the target reduction in SBP was not achieved within 3 minutes,	Primary- *Safety:* percentage of patients in whom the SBP fell below the lower limit of the patient-specific pre-determined target range within 3 minutes of initiating the starting dose (2.0 mg/h). *Efficacy:* percentage of	AE incidence: 40%. Headache & nausea were most common AEs. . SAEs in 11 pts (8.7%). Deaths= 3 (2.7%); all 3 pts had end organ

single-arm study. Duration of Rx= Minimum of 18hrs and a maximum of 96 hrs. Pts followed up for at least 6hrs after stopping study drug infusion. At 12 centres in USA	mmHg assessed on 2 successive occasions 15 minutes apart at baseline; all pts in ICU, CCU or ED. 102 pts had end-organ injury. Age: mean=53yrs, Sex: 61M:65F Race: Caucasian=20, Black=97, Hispanic=8, Asian=1.	clevidipine infusion was to be up-titrated by doubling the dose every 3 minutes to achieve the prespecified target range, but not to exceed the maximum infusion rate of 32.0 mg/h. Clevidipine was to be infused for a minimum duration of 18 hours and a maximum of 96 hours. If the target BP was not attained or maintained, the use of alternative IV antihypertensive agent(s) was allowed, with or without stopping clevidipine infusion. If appropriate, patients were to be transitioned to an oral antihypertensive agent; this was performed by initiating oral therapy approximately 1 hour before the anticipated cessation of clevidipine infusion.	patients who reached the target SBP range within 30 minutes of the initiation of infusion. Secondary- Change in heart rate during the 30-minute period from initiation of infusion; Mean and median dose of clevidipine during the treatment period; proportion of patients who successfully transitioned to oral antihypertensive therapy; Safety of prolonged infusion of clevidipine (>18 hours) assessed according to clinical laboratory parameters including lipid profiles and AEs; Time to attainment of 30-minute SBP target range	damage; 1 death during study & 2 other deaths were 9-11 days after end of study. Discontinuations due to AEs= 6pts (4.8%). Median % change from baseline in HR was +13.2%. supraventricular tachycardia in 2 pts. No other clinically relevant changes in laboratory parameters; lipid (including TG levels did not show sig changes).

Clevidipine was to be infused at an initial rate of 2.0 mg/h for the first 3 minutes. Thereafter, titration was to proceed at the discretion of the investigator by doubling the dose every 3 minutes in order to achieve the patient-specific predetermined SBP target range or up to a maximum of 32.0 mg/h. Clevidipine infusion was allowed to be titrated upwards or downwards during the first 30 minutes in order to achieve/maintain the SBP within the target range. If the desired blood pressure-lowering effect was not attained or maintained during the 30 minutes after start of infusion, an alternative IV antihypertensive agent was allowed to be used, with or without stopping clevidipine infusion. The choice of alternative agent was to be as per institutional practice. Patients who received an alternative antihypertensive agent along with clevidipine were to be continued in the study. Beyond the first 30-minute treatment period, the investigator was allowed to alter the desired SBP target range as necessary to achieve the desired long-term SBP for each patient over the course of the remaining treatment period. The clevidipine infusion rate could be maintained or further titrated (as described above) to achieve the long-term SBP target. Clevidipine infusion was to be administered continuously for a minimum duration of 18 hours and a maximum duration of 96 hours. Due to lipid load restrictions, the total amount of lipid administered was not to exceed 2.5 g/kg per 24-hour period. During the 18- to 96-hour treatment period with clevidipine, patients were to be transitioned to oral antihypertensive treatment as necessary. The transition to an oral antihypertensive agent was to be undertaken approximately 1 hour before the anticipated cessation of clevidipine infusion, but no earlier than the 18-hour time point.

Efficacy endpoints

There were two primary endpoints of this trial, one each to evaluate safety (the percentage of patients in whom the SBP fell below the lower limit of the patient-specific[*], prespecified

[*] In most patients who present with severe hypertension, rapid or extreme reduction in blood pressure may markedly reduce organ blood flow, leading to ischemia and infarction. To avoid excessive or unsafe drops in pressure, the investigator determined an individualized SBP target range based on the patient's medical history and physical examination. The SBP target range was prespecified and recorded using an Interactive Voice Recording System before initiating clevidipine infusion. The range varied from

target SBP range at the initial dose (2.0 mg/h) within 3 minutes of the initiation of the infusion) and efficacy (the percentage of patients who reached the prespecified target SBP range within 30 minutes of the initiation of the infusion).

Blood pressure assessments were made before treatment, at 3 minutes after the start of clevidipine infusion, before each clevidipine infusion titration, and 3 minutes after each clevidipine infusion titration. Blood pressure was assessed every 15 minutes for 2 hours after the target SBP was reached, then hourly until the infusion was discontinued.

The secondary endpoints were: Change in heart rate within the first 30 minutes (HR assessments were made concomitantly with blood pressure assessments); Mean and median dose during clevidipine infusion; Successful transition to oral antihypertensive treatment; Incidence of AEs and SAEs and the time to attainment of 30-minute SBP target range.

To determine if response or tolerability differed based on end-organ injury status, this study summarized the study endpoints by the subset of patients who had and did not have end-organ injury. For the purposes of this study, end-organ injury was defined as evidence of at least one of the following findings: hypertensive changes on fundoscopy; left ventricular hypertrophy observed on an ECG; acute congestive heart failure; renal dysfunction; proteinuria or haematuria; acute focal neurological signs; positive troponin or CK-MB and/or ischemic ECG changes (unstable angina).

The following populations were considered in the statistical analysis of this study:

-Intent-To-Treat (ITT) Population which included all patients who enrolled into the trial and ITT analysis was used to assess potential selection bias.

- Modified Intent-to-Treat (mITT) Population included all patients who enrolled into the trial and whose SBP was above their prespecified target range at the time of study drug initiation. This was the primary population for efficacy analyses.

- Safety Population: All patients who received study drug infusion regardless of infusion duration. This population was the primary population for safety analyses.

- Extended Exposure Subset (EES) Population was a subset of the safety population defined as all patients who received continuous study drug infusion for at least 18 hours[*].

This study was designed without formal calculation of sample size. No statistical hypothesis testing was planned.

Results

The study population represented a high-risk patient population with severe hypertension. Over 95% of the safety population had a history of hypertension, 81% of patients had end organ injury, 77% of patients were African American (black) and 51% were women, 31.0% had a history of prior hospitalization for hypertension, 36.5% had dyslipidaemia and 31% had diabetes. In general, patients who had end organ injury were similar to those without end-organ injury with regard to demographic characteristics and baseline blood pressure. As expected, a history of renal disease, congestive heart failure, stroke, angina pectoris, and chronic obstructive pulmonary disease was more prevalent in the patients with end-organ

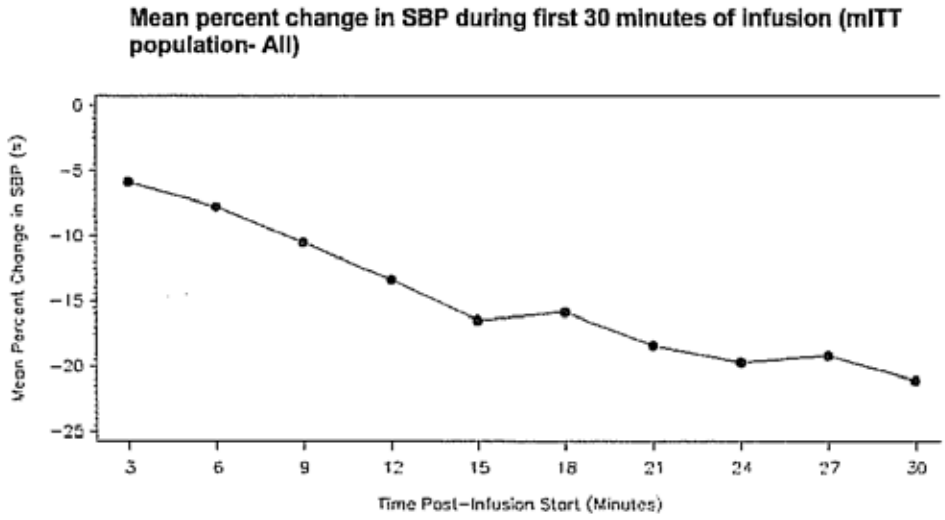
patient to patient, but for each patient, the range was to be not less than 20 mmHg and not more than 40 mmHg from the upper to the lower limit.

[*] Continuous infusion was defined as a period of clevidipine treatment with a maximum of one interruption of 15 minutes; multiple interruptions of 1 minute were allowed. Data from this subset were analyzed to assess safety of prolonged use of clevidipine.

injury than those without. Among the patients who had end-organ injury, left ventricular hypertrophy was most common, followed by renal dysfunction, retinal dysfunction and focal neurological changes. Over 90% of patients received other concomitant medications, the most frequent being heparin agents and proton-pump inhibitors (39% of patients each). Other IV antihypertensive agents were used in the safety population concurrently with clevidipine infusion in 8.7% of patients and used without clevidipine in 6.3% of the patients; 75.4% of patients used oral antihypertensive agents for transition from clevidipine infusion (use within 2 hours before clevidipine cessation) and 34.1% of patients used oral antihypertensive agents as supplementary therapy (use more than 2 hours before clevidipine cessation).

The SBP decreased to within the initial prespecified SBP target range during the first 30 minutes of clevidipine infusion in 89% (104/117) of the mITT population**.** The SBP tended to gradually decrease during the titration period from a mean decrease of 5.9% at 3 minutes to a mean decrease of 21.1% at 30 minutes (Figure 10).

Figure 10: Study TMC-CLV-06-02-velocity



In the subpopulation of patients who received 18 hours of continuous IV clevidipine infusion (Extended Exposure Subset [EES] population), the majority (108/117, 92.3%) were managed without the use of additional IV antihypertensive agents during the 18-hour period.

The BP responses in patients exposed to 32 mg/h of clevidipine (N=38) in the VELOCITY study were examined to assess the benefit, if any, of titration up to this dose. Further decreases in SBP were observed in 24/38 (63.2%) of patients who were up-titrated from 16 to 32 mg/h. The change in SBP observed following up-titration from 8 to 16 mg/h was subtracted from the change observed following up-titration from 16 to 32 mg/h. The median value for this difference was 6.5 mmHg.

In the mITT population, SBP decreased to within the initial SBP target range in a median time of 10.9 minutes. Patients who did not reach target SBP (regardless of whether patients stayed or were withdrawn from the study) were censored from this analysis. There were only 3 patients that did not reach SBP target range. The median time to achieve 15% reduction from baseline was 9.5 minutes. The individualized SBP target range could be modified for patients during the study period. After the initial 30-minute assessment period, the SBP was outside the applicable target range for a median of 21.6% of the overall clevidipine infusion period or conversely, SBP was within the target range for 78.4% of the infusion period. At the 15-minute time points during the first 2 hours of clevidipine infusion (excluding the first 30 minutes), SBP was within the applicable target for 63% to 76% of patients. At every hour after the initial 2 hours to 24 hours of infusion, SBP was within the target range for 57% to 80% of patients, indicating that SBP was controlled in most patients for several hours beyond the initial 30-minute titration period.

Transition to oral antihypertensive therapy within 6 hours after discontinuing clevidipine infusion was successful in 91.3% (115/126) of patients. Of the 11 patients who were categorized as “unsuccessful transition,” three patients were transitioned from clevidipine infusion, but blood pressure was not satisfactorily controlled with multiple oral antihypertensive agents. One patient discontinued clevidipine infusion without the need for oral antihypertensive therapy. Critical medical conditions prevented the use of oral agents in two patients, both of whom later died. The remaining five patients discontinued clevidipine before reaching the 18-hour time.

Results from this study provided evidence that the prolonged infusion of clevidipine (>18 h but <96 h) is well tolerated and effective for the control of blood pressure in high-risk patients with severe hypertension requiring urgent treatment.

Dose-response analysis

The dose-response data from Phase II and III studies support the proposed starting dose of 2 mg/h and titration up to a maximum dose of 32 mg/h. While most patients will respond at doses of approximately 16 mg/h, patients with intact baroreceptor-mediated reflex responses to hypotension (such as those patients not exposed to concomitant beta-blockers or anaesthesia) may require titration to doses towards the higher end of the dose range.

Dose-response in Phase II studies

The Phase II dose-finding study SAD-0003 demonstrated dose-dependent reductions in MAP between 0.05 - 9.58 μg/kg/min (0.24 to 46 mg/h) and that a dose of approximately 2 mg/h (0.3 - 0.4 μg/kg/min) was an appropriate starting dose. There was a statistically significant difference ($p<0.05$) in MAP, SBP and DBP between placebo and all doses of clevidipine, except for 0.05 μg/kg/min ($p>0.05$). Clevidipine was safe and well tolerated up to a dose rate of 9.58 μg/kg/min (approximately 46 mg/h). However, at this highest dose rate, hypotension resulting in discontinuation of study therapy occurred in 28% of patients.

Clevidipine exhibited a linear dose response versus MAP and mean blood concentrations over the dose range of 0.18 -5.48 μg/kg/min (approximately 0.9 - 27 mg/h) in the Phase II, placebo-controlled study SAD-0010.

In study SAD-0004, clevidipine administered concomitantly with oral beta-blockers exhibited dose-dependent reductions in mean arterial BP of 5%, 10%, and 15% at dose rates of 0.06, 0.2 and 0.6 μg/kg/min, respectively (approximately 0.3 mg/h, 1 mg/h, and 3 mg/h).

In study TMC-CLV-06-01, steady-state clevidipine concentrations and percent change from baseline in SBP are directly related at doses between 2.0-16 mg/h.

In SAD-0005, Clevidipine induced a rapid dose-dependent reduction in MAP with no reflex tachycardia in cardiac surgery patients.

In SAD-0006, Lower clevidipine dose rates were required to achieve a 20% reduction in BP during the hypothermic phase of bypass versus pre-bypass.

Dose-response in Phase III studies

In addition to classic Phase II dose-ranging studies, a post-hoc regression analysis of Phase III studies supports an effective dose range of 2 mg/h to 32 mg/h and a linear relationship between clevidipine dose and percent change in SBP at doses up to 20 mg/h. This post-hoc analysis of the dose response in percent change from baseline in SBP was presented for the Phase-III studies and grouped as follows.

• ESCAPE studies (TMC-CLV-03-01 and TMC-CLV-03-02)

• VELOCITY study (TMC-CLV-06-02)

• Combined ESCAPE and VELOCITY studies (TMC-CLV-03-01, TMC-CLV-03-02, and TMC-CLV-06-02)

The percentage change in SBP from baseline to the first SBP measurement after an increase in infusion rate (but before the next dose rate change) was used as the response value to the actual infusion dose rate. As the recommended clevidipine infusion rate ranged from 0 to 32 mg/h, the dose-response analysis was performed on this dose range. Any BP measurements associated with infusion rates greater than 32 mg/h were excluded from the analysis.

ECLIPSE studies were excluded from the analysis because the majority of patients had only 1 data point, in general at low infusion rates, so individual dose-response relationship could not be assessed.

For all three analyses, clevidipine demonstrated a predictable dose response. There was a linear relationship between clevidipine dose and percent change in SBP at doses up to 20mg/h. The dose-response relationship observed in the ESCAPE studies, the VELOCITY study and the combined ESCAPE and VELOCITY studies predicts an approximate reduction in SBP of 1.0% per 1 mg/h incremental increase in dose level. The dose-response relationship is seen to plateau beyond 20 mg/h. Titration up to 32 mg/h was examined in the VELOCITY study. A significant number of patients experienced further decreases in SBP at doses above 20 mg/h up to 32 mg/h. The change in SBP observed following up-titration from 8 to 16 mg/h was subtracted from the change observed following up-titration from 16 to 32 mg/h. The median value for this difference was 6.5 mmHg. Further decrease in SBP was obtained in 24 out of 38 patients (63.2%) who were up-titrated from 16 to 32 mg/h. These data suggest that a significant number of patients would experience further decreases in SBP at doses above 20 mg/h up to 32 mg/h, although this was evaluated only in patients with severe hypertension (not evaluated in perioperative hypertension or essential hypertension).

Summary of efficacy

The main evidence for efficacy of clevidipine for the proposed indication was evaluated in 214 patients in the 2 double-blind, placebo-controlled, Phase III ESCAPE studies (104 pre-operative and 110 post-operative patients with hypertension). In both the ESCAPE studies, clevidipine infusion was associated with statistically and clinically significant greater treatment success (or reduced incidence of bailout) compared with placebo during a 30-minute evaluation period. Clevidipine demonstrated a rapid onset of effect; the median time to achievement of a >15% reduction in SBP from baseline in patients treated with clevidipine was 5 to 6 minutes.

Results from Phase III VELOCITY study (involving 126 patients) provided evidence that the prolonged infusion of clevidipine (>18 h but <96 h) is well tolerated and effective for the control of blood pressure in high-risk patients with severe hypertension requiring urgent treatment.

The open-label, Phase III ECLIPSE studies provided supportive evidence of efficacy of clevidipine in 1506 patients with hypertension following cardiac surgery. Although, clevidipine appeared to provide better BP control compared with GTN and SNP, these results should be interpreted with caution due to open-label nature of study and lack of pre-defined non-inferiority analyses. ECLIPSE-NIC showed comparable control of BP with clevidipine and nicardipine.

Three Phase II studies demonstrated some evidence of rapid reduction in MAP with clevidipine in 95 patients with mild to moderate essential hypertension. Furthermore, there was rapid reversal of effect and no evidence of rebound hypertension following cessation of clevidipine infusion.

Six Phase II studies in 337 patients with perioperative hypertension provided evidence of therapeutic dose range (0.18 to 3.19ug/ml) and also demonstrated efficacy of clevidipine in treatment of perioperative hypertension.

Collectively, the Phase II and III studies examining dose-response confirm that an appropriate starting dose of clevidipine is 2 mg/h. Furthermore, a linear relationship exists between clevidipine dose, reduction of BP and clevidipine blood concentrations, including a linear relationship between clevidipine dose and percent change in SBP at doses up to 20

mg/h; however, there is a flattening of the dose-response relationship at doses greater than 20 mg/h and up to 32 mg/h. Although, the effective clevidipine dose range is 2 to 32 mg/h, most patients will achieve the desired therapeutic response at doses≤16 mg/h and only some patients with severe hypertension may require doses up to 32 mg/h.

The dose-response relationship observed in the combined ESCAPE and VELOCITY studies predicts an approximate reduction in SBP of 1% per 1 mg/h incremental increase in dose level.

The infusion of clevidipine over a 72 hour period across the dose range 2.0 to 16.0 mg/h demonstrated a general correlation between steady-state clevidipine concentrations and percent change from baseline in systolic blood pressure (SBP) across the dose levels of clevidipine with no evidence of rebound hypertension. Offset of effect, when assessed as full recovery to baseline BP, was rapid (approximately 5-15 minutes) at doses from 2 -16 mg/h.

Clevidipine infusion administered continuously for up to 72 hours across the entire therapeutic dose range was not associated with the development of tolerance. The potential for the development of acute tolerance effects was evaluated in TMC-CLV-06-01 and VELOCITY.

Safety

Overall drug exposure and patient populations evaluated for safety

Clevidipine clinical development included 19 studies, with 99 healthy subjects and 1307 hypertensive patients who received at least one dose of clevidipine (1406 total exposures).

The primary assessment of safety was based on pooled data from 15 Phase II and III studies of 1307 clevidipine-treated patients: 11 studies of perioperative hypertension (six Phase II and five Phase III studies; N=1099 clevidipine-treated patients), one Phase III study of patients with severe hypertension (N=126 clevidipine-treated patients), and three Phase II studies of patients with essential hypertension (N=82 clevidipine-treated patients).

Of these 15 prospective studies in hypertensive patients, only two were cross-over studies. A separate analysis of the 13 parallel treatment group studies (excluding the two crossover studies) was not done, but this is not likely to have significant impact on the safety results given that few patients were enrolled in the two crossover studies (SAD-0005: 14 patients and SAD-0010: 21 patients).The six Phase III studies contributed the most patients and data of importance, including 992 clevidipine-treated patients. Specifically, the three ECLIPSE studies (TMC-CLV-03-03; TMC-CLV-03-04; and TMC-CLV-03-05) were safety studies in cardiac surgery patients with perioperative hypertension and the primary objective of these studies was to compare the safety of clevidipine (N=752) to comparators GTN, SNP or NIC, respectively. The two ESCAPE studies (TMC-CLV-03-01; TMC-CLV-03-02) were pivotal, placebo-controlled efficacy studies in cardiac surgery patients with perioperative hypertension comparing clevidipine (N=114) to placebo that also evaluated safety. The VELOCITY study (TMC-CLV-06-02) evaluated the effective and safe use of clevidipine (N=126) in severe hypertension and did not have a comparator.

Safety parameters

The major safety assessments of the six Phase III studies are summarised in Table 23.

Table 23: Major Safety Assessments for Phase III Studies

safety variable	ECLIPSE NTG	ECLIPSE SNP	ECLIPSE NIC	ESCAPE 1	ESCAPE 2	VELOCITY
CEC-adjudicated data for death, MI, stroke	X	X	X	N/A	N/A	N/A

and/or renal dysfunction						
Haemodynamics	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X
Haematology/serum biochemistry	X	X	X	X	X	X

Additional safety assessments that were performed include evaluations of vital signs, adverse events (AEs) of special interest (reflex tachycardia, hypotension, hypovolaemia, oedema, and blood-borne infections), AEs onset up to 1 hour post termination of study drug, AEs and use of β-blocker agents, laboratory tests and subgroup analyses. The CEC adjudicated endpoints, AEs onset up to 1 hour post termination of study drug, and 'BP below the pre-specified range'[*] were assessed only for the ECLIPSE studies.

AEs were included in the safety analyses from the start of the surgical procedure or start of the study drug infusion, whichever occurred first, until 7 days after this time, with exceptions for serious adverse events (SAEs) which started at any time up to 30 days post-surgery start for perioperative studies or 30 days post-study drug initiation for all other clinical studies which were included in the safety analyses. An AE with onset after discontinuation of study drug was allocated to the last study drug administered if the AE occurred within 7 days (or 30 days for SAEs) after the beginning of the surgery procedure or infusion start, whichever occurred first. Treatment-emergent adverse events (TEAEs) were defined as AEs with onset after the start of the study drug infusion and not more than 7 days after start of the surgical procedure or start of the infusion. If a pre-treatment AE worsened in severity after the start of study drug administration, the AE was considered to be treatment-emergent (if an AE had an unknown or missing onset the AE was still considered treatment-emergent).

Safety in healthy subjects

In all healthy volunteer studies, 84.8% of subjects were males, 70.7% of subjects treated with clevidipine were white and all were <65 years old. In healthy subjects the overall median infusion duration was 1 hour and the median average infusion rate was 15.72 mg/h. This relatively brief exposure reflected the nature of early phase studies in which short-term dose tolerability was assessed.

Approximately 69% of healthy subjects who received clevidipine and 17% of subjects who received placebo had at least one TEAE. The most common TEAEs in clevidipine-treated subjects were headache and flushing. There were no deaths or SAEs in healthy subjects. Three healthy volunteers who received clevidipine discontinued study drug due to one or more of the following AEs: nausea, vomiting, or headache.

In **SAD-0001**, clevidipine was well tolerated and safe in 46 healthy volunteers up to a dose rate of at least 21.96 μg/kg /min (106 mg/h). The effect of clevidipine on BP was marginal, which was most likely due to the compensatory baroreflex action in this population of healthy volunteers.

SAD-0018 was a PK study of clevidipine in healthy male subjects during and after a 24-hour and a 20-minute intravenous infusion. There were no reports of serious AEs. One patient

[*] *BP below the pre-specified range*: In the three ECLIPSE studies (TMC-CLV-03-03, TMC-CLV-03-04, and TMC-CLV-03-05), the undesirable BP-lowering effect caused by clevidipine was assessed by calculating the total area of the systolic blood pressure (SBP)-time curve that fell below the lower limit of the prespecified range in perioperative cardiac surgery patients.

discontinued study drug due to multiple AEs. Flushing and headache were the most commonly reported AEs. Clevidipine is a high-clearance drug with a small volume of distribution, resulting in extremely short half-lives in healthy volunteers. The initial rapid increase in the arterial blood concentrations and the short equilibrium time between the blood and the biophase suggest that clevidipine can be rapidly titrated to the desired effect.

TMC-CLV-05-01 was a single-blind prospective randomised crossover study of clevidipine in 54 healthy volunteers to determine ECG safety; results from this study demonstrated that supratherapeutic concentrations of clevidipine and its metabolite were associated with statistically significant, albeit modest, decreases of QTcF and QTcEi. The maximal mean, control-subtracted changes of QTcF and QTcEi were less than 5 and the upper bounds of the 95% confidence interval (CI) 1-sided were less than 10 msec. Moxifloxacin administration was associated with the expected rise of ddQTcF with the lower bound of its 95% CI 1-sided greater than 0 msec, thus confirming the sensitivity of the assay. No rise of ddQTcF or ddQTcEi was observed as the concentration of clevidipine or H152/81 increased. Most of the associated findings could be attributed to the higher HRs during clevidipine therapy. Additional ECG findings included the expected statistically significant HR rise (maximal at 24.1 bpm), mild PR prolongation (maximal 13.2 msec), and minor QRS shortening (minimum of -4.9 msec) (p values of < 0.0001, 0.0013, and 0.0022, respectively). Other than the HR, these changes were of no clinical significance. There were no deaths and no reports of serious AEs. Two patients withdrew from study due to AEs. The most commonly reported treatment- related AEs were: headache, nausea, dizziness, and flushing.

Safety in patients

Drug exposure

Safety in target patient population was evaluated in distinct groups: 'All hypertensive' patients, 'Phase III studies' and by 'type of hypertension', that is, perioperative hypertension, severe hypertension and essential hypertension.

Hypertensive patients received clevidipine doses over a wide range up to 60 mg/h. The median initial infusion rate of clevidipine in hypertensive patients was 2.0 mg/h. The median average infusion rate was 3.99 mg/h and the median overall infusion duration was 6.44 hours.

Eighty percent (994/1240) of the patients in the studies for treatment of hypertension were exposed to an average clevidipine infusion rate of≤8 mg/h. An average infusion rate >8 mg/h was administered to only 19.8% (246/1240) of hypertensive patients and most patients achieved the desired therapeutic response at doses up to 16 mg/hour. A higher proportion of patients (47.6%; 60/126) in the severe hypertension group received an average infusion rate >8 mg/h. Among hypertensive patients, there were 68 patients who were treated with a dose rate between >16 and ≤32 mg/h and 5 patients that received a dose >32 mg/h. The infusion rate could not be derived in 5.1% (67/1307) of patients.

The majority (92%, N=1199/1307) of hypertensive patients received a continuous infusion for <24 hours; an additional 93 patients received continuous clevidipine infusions between 24 and 72 hours. Of the patients who received a continuous infusion of clevidipine for≥48 hours, 92% (47/51) were enrolled in the pharmacokinetic/pharmacodynamic study in essential hypertension (TMC-CLV-06- 01) for which the protocol required dosing for 72 hours.

In the Phase III perioperative hypertension studies, the median initial clevidipine infusion rate and average infusion rate were 2.05 mg/h and 3.48 mg/h, respectively. The median total dose of clevidipine was 10.66 mg. The median overall infusion duration and on-drug infusion duration for the clevidipine group was 4.92 hours and 3.03 hours, respectively. In the severe

hypertension study (TMC-CLV-06-02), the median initial clevidipine infusion rate and average infusion rate were 2.00 mg/h and 7.88 mg/h, respectively. The median total dose of clevidipine was 168.17 mg. The median overall infusion duration and on drug infusion duration for the clevidipine group were each 20.66 hours.

In the VELOCITY study, patients with severe hypertension were exposed to continuous clevidipine infusion for a median duration of 1239.5 minutes (20.7 hours). The total mean and median total doses infused were 206 mg and 168.2 mg, respectively. Most patients (122/126, 96.8%) received clevidipine through a peripheral vein. Of the safety population, 92.9% (117/126) were exposed to at least 18 hours of continuous clevidipine infusion and constituted the EES population.

Data for infusion duration and total infusion volume were collected for the control treatments**,** but dose calculations were not possible because active comparator agents were reconstituted and diluted to different concentrations in different institutions and these details were not captured in the case report forms. Overall, the exposure achieved in clevidipine-treated patients was appropriate to provide a valid safety assessment compared to the control treatments. The pattern of use of the three active comparator drugs (GTN, SNP or NIC) highlights some similarities but also some important differences between these agents. GTN was infused for longer with median on-drug duration 9.60 hours (this is likely to be due to the use of GTN as an anti-ischemic agent following cardiac surgery, rather than for its antihypertensive properties) and the total infusion volume was noticeably greater in the NIC treatment group (163.8 mL) despite a similar value to clevidipine for on-drug duration (4.58 hours). NIC must be reconstituted to generate a 250 mL solution (0.1 mg/mL). This dilution results in a higher average infusion rate in NIC-treated patients and a greater infusion volume. SNP was associated with the smallest values for on-drug duration and infusion volume delivered.

Baseline characteristics of the safety populations

Of the hypertensive patients treated with clevidipine in all studies, 71.6% were males, 76.4% were white, 47.4% were ≥65 years old and the mean body mass index was 29.2 kg/m2. There were 232 patients ≥75 years of age. Overall, the demographics of the comparator groups were similar except for a higher percentage of black patients treated with clevidipine (16.0%) compared to the placebo group (4.4%) and active comparators group (7.9%). There were a lower percentage of clevidipine-treated patients (7.6%) in the race category of 'other' compared to placebo (13.8%) or the active comparators group (8.8%). Of patients with severe hypertension treated with clevidipine, 77% were black (reflecting the greater prevalence of severe hypertension in black patients).

The baseline characteristics of hypertensive patients were generally similar in the clevidipine, placebo and all active comparators groups. The majority of all hypertensive patients (84%) and 100% of the all active comparators patients were studied in the perioperative cardiac surgery setting. The type of surgery was similar across the study groups. A higher percentage of hypertensive clevidipine-treated patients (15.3%) and all active comparator patients (16.7%) had congestive heart failure (CHF) at baseline compared to those receiving placebo (8.2%). Approximately one-third of hypertensive patients were categorised with Stage 1 hypertension. Patients enrolled in the VELOCITY study (TMC-CLV-06-02) contributed 59.3% (118/199) of the patients with Severe Stage 2 hypertension. About 40% of patients exposed to clevidipine had abnormal renal function and 6% had elevated serum bilirubin and/or elevated liver enzymes at baseline. There was a high prevalence of diabetes (31.7%), peripheral vascular disease (12.4%), heart failure (15.3%), and stroke (10.0%).

By type of hypertension: For clevidipine-treated patients in the 'perioperative group', 74.4% were males, 83.4% were white, 51.9% were ≥65 years old, and the mean body mass index was 29.1 kg/m^2. The demographics of the treatment groups were similar, except 40.6% of patients in the placebo group were ≥65 years old and 8.9% of the clevidipine group (compared with 2.3% of the placebo group) were black. In the perioperative hypertension group, placebo-treated patients had a higher mean SBP (159.3 mmHg) than clevidipine-treated patients (143.0 mmHg) or the all active comparators group (138.3 mmHg). A similar pattern was observed for the mean DBP where it was 76.1, 70.7, and 69.2 mmHg for placebo, clevidipine, and all active comparators group, respectively. Clevidipine-treated, placebo-treated, and all active comparator patients had similar incidences of abnormal renal and liver function tests and similar incidences of diabetes, CHF, stroke, and peripheral vascular disease.

A notably different population was found for clevidipine-treated patients in the 'severe hypertension group' compared with the perioperative group: 51.6% were females (compared with 25.5% in perioperative group), 77.0% were black (compared with 8.9% in perioperative group), and 76.2% were <65 years old (compared with 48.1% in perioperative group). The mean body mass index was similar to the perioperative group (30.0 kg/m^2). Clevidipine-treated patients in the severe hypertension group had a notably higher mean SBP (202.1 mmHg) and mean DBP (111.0 mmHg) compared to either the perioperative (SBP, 143.0 mmHg; DBP, 70.7 mmHg) or essential hypertension (SBP, 161.5 mmHg; DBP, 92.8 mmHg) groups. Over 90% of patients in the severe hypertension group had Severe Stage 2 hypertension and 13.5% had severe renal impairment. The incidences of diabetes, CHF, stroke, and peripheral vascular disease were similar to the perioperative group.

For clevidipine-treated patients in the 'essential hypertension group', 69.5% were males, 75.6% were white, 24.4% were ≥65 years old, and the mean body mass index was 30.3 kg/m^2. The demographics of the placebo group were similar except that a higher percentage of placebo-treated patients were ≥65 years old (34.6% placebo vs 24.4% clevidipine). For clevidipine-treated patients in the essential hypertension group, the mean SBP (161.5 mmHg) and DBP (92.8 mmHg) were similar to the placebo group (SBP, 159.7 mmHg; DBP, 92.4 mmHg). Overall, clevidipine-treated essential hypertensive patients were similar to placebo in hypertensive severity, renal impairment, liver function status, and the incidence of CHF, stroke, and peripheral vascular disease. There was a higher incidence of diabetes in clevidipine-treated patients (18.3%) compared with placebo patients (7.7%).

Phase III studies: Analysis of the Phase III studies as a group showed results similar to the peri-operative and severe hypertension groups already discussed above under the subsection of by type of hypertension for SBP, DBP, stage of hypertension, renal and liver function status, and disease subgroups.

Adjudicated endpoints, unwanted hypotension, rebound hypertension, and heart rate (reflex tachycardia)

Adjudicated endpoints (death, MI, stroke or renal dysfunction)

In the 3 ECLIPSE studies, the incidences of death, MI, stroke, or renal dysfunction at 30 days (as adjudicated by a blinded CEC) were similar in clevidipine-treated and comparator-treated patients in the three Phase III ECLIPSE studies (Table 24). The analysis using the crude rates demonstrated consistent results and confirmed the robustness of the findings.

Table 24: CEC-adjudicated Events of Death, Stroke, Myocardial Infarction and/or Renal Dysfunction from ECLIPSE Studies (hypertensive patients)

Term	Clevidipine (N=752)	All Active Comparators (N=754)	Difference (%) estimate 95% CI
Any CEC-adjudicated event, n (%)	77 (10.7)	86 (11.8)	-1.1 (-4.37, 2.13)
Death	20 (2.8)	28 (3.6)	-1.0 (-2.90, 0.78)
Stroke	8 (1.1)	12 (1.7)	-0.6 (-1.80, 0.66)
Myocardial infarction	16 (2.3)	17 (2.4)	-0.1 (-1.70, 1.46)
Renal dysfunction	56 (7.9)	56 (7.9)	0.0 (-2.82, 0.92)
Death or stroke	27 (3.8)	36 (4.9)	-1.1 (-3.28, 0.92)
Death or MI	35 (4.9)	38 (5.2)	-0.3 (-2.61, 1.90)
Death or stroke or MI	41 (5.7)	46 (6.3)	-0.6 (-3.06, 1.84)

The above comparison of treatment groups was repeated for subgroups age, gender, race, hypertensive severity, renal function status, liver function status, duration of clevidipine infusion and total clevidipine dose. No clinically meaningful differences between treatment groups were found in any of these subgroup analyses. The incidence of one or more event increased in patients with moderate or severe renal dysfunction. However this observation was of similar magnitude across all treatment groups

Unwanted hypotension

Clevidipine treatment was not associated with an excess incidence of 'overshoot' or unwanted hypotension in clinical trials of hypertensive patients. The incidence of unwanted hypotension was assessed in three analyses as follows:-

(1) Safety of the starting dose (2 mg/h): In patients with severe hypertension (VELOCITY study), one of the co-primary endpoints was the incidence of overshoot of BP below the lower limit of the prespecified SBP target range following initiation of clevidipine infusion at the starting dose (2 mg/h). The results of this analysis revealed that only 2 of the 126 patients who were dosed with clevidipine had SBP measurements below the range at 3 minutes after the start of infusion. Both of these patients continued clevidipine infusion for longer than 18 hours, with no adverse clinical consequences reported.

(2) Incidence of the AE terms associated with 'hypotension': The AE term 'hypotension' and terms with similar meaning to hypotension were reported in 14.5% of 'all hypertensive patients' treated with clevidipine, compared with 15.5% in the all active comparators group. In the same patient population, 2.1% of clevidipine-treated patients discontinued the infusion due to hypotension, compared with 1.7% of patients in the combined active comparators group.

(3) BP below the pre-specified range: Clevidipine-treated patients had a low incidence and severity of hypotension as reflected by the AUC values below the prespecified range. The median value for total AUC_{SBP-D} was 0 mmHg. min/h for clevidipine and for the combined active comparators (GTN, SNP, and NIC) in the three Phase III ECLIPSE studies. The mean value in clevidipine-treated patients was 1.99 mmHg × min/h compared with 4.29 mmHg × min/h in the combined active comparators group. This difference appears to have been largely influenced by patients treated with SNP (mean value 8.41 mmHg × min/h); the results in GTN and NIC-treated patients were similar to those observed in the clevidipine treatment group.

Rebound hypertension

The potential for rebound hypertension was studied specifically in the PK/PD study (TMC-CLV- 06-01), in which 61 patients with mild to moderate essential hypertension were treated continuously with clevidipine for 72 hours. Recovery of BP was followed carefully for 4 hours (at least every 15 minutes) following discontinuation of clevidipine infusion. There was no evidence of rebound hypertension following termination of the clevidipine infusion with SBP returning to baseline following cessation of treatment.

The majority (57.1%) of 'perioperative patients' who received clevidipine postoperatively for the treatment of hypertension had a maximum increase of no more than 10% in SBP from the last measurement on study drug to 1 hour after termination of study drug. About 10% of patients had maximum increases greater than 30%.

'All Hypertensive patients': Due to the rapid clearance of clevidipine from circulation, the observed increase in SBP 1 hour after the cessation of infusion reflects the complete offset of effect. The maximum increases in SBP from the last measurement on study drug to 1 hour after termination of study drug were similar in clevidipine and active comparator treatment groups. For the clevidipine group and the all active comparators group, 10-11% of patients had greater than 30% increase in SBP from the last measurement on study drug to 1 hour after termination of study drug, compared with 3.1% of the placebo group. The median percentage change in SBP from last measurement on study drug to within 1 hour of stopping study drug infusion was small in all treatment groups: clevidipine (7.8%); all active comparators group (3.9%); and placebo (4.5%) (Table 25).

Table 25: Systolic Blood Pressure: Maximum Increase within One Hour Post-termination of Study Drug Infusion (hypertensive patients)

Variable	**Clevidipine (N=1168)**	**Placebo (N=108)**	**All Active Comparators (N=769)**
Number of patients with an assessment at both last BP measurement on study drug and at 0-1 h after treatment	944 (100.0)	96 (100.0)	594 (100.0)
Maximum of individual values that increased 0-1 h after treatment stopped, n (%)			
≤10%	539 (57.1)	64 (66.7)	403 (67.8)
>10% - 20%	184 (19.5)	20 (20.8)	78 (13.1)
>20% - 30%	119 (12.6)	9 (9.4)	51 (8.6)
>30% - 40%	54 (5.7)	2 (2.1)	21 (3.5)
>40% - 50%	25 (2.6)	1 (1.0)	22 (3.7)
>50%	23 (2.4)	0 (0.0)	19 (3.2)

When analysed by type of hypertension, maximum increases in SBP in the perioperative hypertension group were similar in the clevidipine and the all active comparators groups, with only 11.5% of clevidipine and 10.4% of all active comparators patients having a greater than 30% increase in SBP from the last measurement on study drug to 1 hour after termination of study drug, compared with 4.3% of the placebo group. In the severe hypertension group, only 4% of patients had a greater than 30% increase in SBP within 1 hour after termination of study drug). In the essential hypertension group, 21.3% of the clevidipine group had a maximum increase in SBP from the last measurement on study drug to 1 hour after termination of study drug of no higher than 10% compared to 53.8% of patients in the placebo group; and 15.1% of patients in the clevidipine group had a greater than a 30% increase in SBP compared with 0.0% in the placebo group. When analysed by type of hypertension, in the perioperative and severe hypertension groups, the median percentage change in SBP from last measurement on study drug to within 1 hour of stopping study drug infusion was small (2.7-7.2%) in all treatment groups. However, in the essential hypertension group, the median percentage change was 17.5% in clevidipine-treated patients compared with 9.5% for placebo**.**

In the Phase III perioperative studies, the maximum increases in SBP from the last measurement on study drug to 1 hour after termination of study drug were similar in clevidipine and active comparator treatment groups. For the clevidipine group and the all active comparators group, 10 to 12% of patients had greater than 30% increase in SBP from the last measurement on study drug to 1 hour after termination of study drug, compared with 6.4% of the placebo group. Only 4.0% of patients in the severe hypertension group had a greater than 30% increase. The median percentage change in SBP from last measurement on study drug to within 1 hour of stopping study drug infusion was small in all perioperative hypertensive groups: clevidipine (5.7%); all active comparators group (3.8%); and placebo (2.3%). The median percent change was 7.2% in the severe hypertension group.

Reflex tachycardia

The median value for the maximum individual HRs in the hypertensive study population during the first hour of study drug infusion was similar for clevidipine and the active

comparators groups, but higher than the placebo group. The median percentage increase in HR from baseline to maximum on-treatment assessment was higher in the all active comparators group (36.8%) than in the clevidipine group (25.3%), and, as expected, lower in the placebo group (4.7%).

By type of hypertension: In the perioperative group, the median value of the maximum on-treatment HR was lowest in the placebo group (89.5 beats/min) compared to 98 beats/min for the clevidipine group and 102 beats/min for all active comparators group. The median percentage increase from baseline to maximum HR value was largest for the all active comparators group (36.8%) compared with 25.0% for the clevidipine group and 3.7% for the placebo group.

The median value of the maximum on-treatment HR for the severe hypertension group was 105 beats per minute (BPM) and the median percentage change from baseline to the maximum on-treatment assessment was 29.5%. This percentage change was similar to clevidipine-treated patients in both the perioperative (25.0%) and essential (26.5%) hypertension groups. For the essential hypertension group, the median value of the maximum on-treatment HR (90 bpm) and the median percentage change from baseline to the maximum on-treatment assessment (26.5%) was notably higher than placebo (75.5 bpm and 14.5%, respectively) but similar to clevidipine-treated patients in the perioperative and severe hypertension groups.

Phase III studies: The results were similar in the Phase III studies. The median value of the maximum on-treatment HR was similar for the clevidipine group (99 bpm) and combined active comparators group (102 bpm) of the perioperative studies, as well as for the clevidipine-treated patients in the severe hypertension study (105 beats/min).

The combined active comparators group had the highest percent increase (37.1%) from baseline to maximum HR value compared with 27.9% for the perioperative clevidipine group and 29.5% for the severe hypertension clevidipine group

Maximum increase in heart rate

All Hypertensive patients: A greater than 30% maximum increase in HR from baseline to within 1 hour post initiation of study drug infusion was observed in 27.6% of the clevidipine group, 38.2% of all active comparators group, and 5.5% of the placebo group

By type of hypertension: In the perioperative group, 28.6% of the clevidipine-treated patients, 38.2% of patients in the combined active comparators group, and 6.4% of placebo-treated patients had greater than 30% maximum increase in HR; this magnitude of HR increase occurred in 27.8% of the severe hypertension group. In the essential hypertension group, 16.9% of clevidipine-treated and 0.0% of placebo-treated patients had a greater than 30% maximum increase in HR.

Phase III studies: In the Phase III perioperative studies, 31.2% of the clevidipine group and 38.9% of the all active comparators group had greater than 30% maximum increase in HR; this magnitude of HR increase occurred in 27.8% of patients treated with clevidipine in the severe hypertension study

AEs

Incidence of AEs in various safety populations

The majority of TEAEs were assessed as not treatment-related* in **'all hypertensive'** patients regardless of treatment group. However, treatment-related TEAEs were reported in a larger

* Subjective investigator assessment of treatment-related TEAEs was collected on the AE case report form (CRF).

proportion of patients who received clevidipine (19.1%) compared to all active comparators (10.5%). Cardiac disorders and vascular disorders were the System Organ Classes (SOCs) with the highest incidence of treatment-related TEAEs for the clevidipine-treated and the all active comparators groups.

The most common (≥5% for clevidipine) TEAEs for clevidipine-treated and the combined active comparator groups in hypertensive patients were incision site complications (33.8% and 52.2%, respectively) and atelectasis (31.3% and 37.9%, respectively).

The **perioperative patients** comprised 84% (1099/1307) of the clevidipine-treated hypertensive patients. In the 'perioperative hypertension group', the overall incidence of TEAEs in patients treated with clevidipine (92.4%) was similar to that of the all active comparators group (95.4%) but higher than the placebo group (64.7%). The SOCs with the highest percentage of patients with TEAEs in the clevidipine, placebo, and all active comparators groups were cardiac disorders and respiratory, thoracic, and mediastinal disorders. The most common incidence of TEAEs in clevidipine-treated patients in the perioperative studies were incision site complications (40.2%), atelectasis (37.2%), and atrial fibrillation (30.4%); similar incidences for atelectasis (37.9%) and atrial fibrillation (30.8%) and a slightly higher incidence of incision site complications (52.2%) were reported in the all active comparators group. Atrial fibrillation, pyrexia, and nausea were the most common TEAEs in the placebo group.

In the perioperative treatment group, the majority of TEAEs were assessed as not treatment-related. The incidence of treatment-related TEAEs was higher in clevidipine-treated patients (17.7%) than in the all active comparators group (10.5%) or placebo (3.0%). Cardiac disorders and vascular disorders for the clevidipine-treated and the all active comparators groups and investigations for the placebo group were the SOCs with the highest incidence of treatment-related TEAEs.

In the **severe hypertension group**, the overall incidence of TEAEs in patients treated with clevidipine was 47.6%; the SOCs with the highest percentage of patients with TEAEs were nervous system disorders (14.3%), and general disorders and administration site disorders (11.1%); these percentages were similar to or lower than those reported in the Phase III perioperative group. In the severe hypertension group, TEAEs with the highest incidence were headache (7.1%), nausea (4.8%), and vomiting (3.2%) in clevidipine-treated patients (Table 26). The incidence of treatment-related TEAEs was 9.5% in clevidipine-treated patients in the severe hypertension group. The SOCs with the highest incidence of treatment-related TEAEs in patients with severe hypertension were investigations (3.2%). This was followed by cardiac disorders, general disorders and administration site conditions, and gastrointestinal disorders (2.4% each).

Table 26: Most Common (≥3%) Treatment Emergent Adverse Events in Patients with Severe or Essential Hypertension

System Organ Class **Preferred Term**	**Essential Hypertension**		**Severe Hypertension**
	Clevidipine (N=82)	**Placebo (N=26)**	**Clevidipine (N=126)**
Injury. Poisoning and procedural complications			
Infusion site bruising	3 (3.7)	0 (0.0)	0 (0.0)
General disorders and administrative site conditions			
Pyrexia	3 (3.7)	0 (0.0)	0 (0.0)
Infusion site swelling	5 (6.1)	1 (3.8)	0 (0.0)
Feeling hot	5 (6.1)	0 (0.0)	1 (0.8)
Infusion site erythema	4 (4.9)	1 (3.8)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	4 (3.2)
Gastrointestinal disorders			
Nausea	6 (7.3)	0 (0.0)	6 (4.8)
Vomiting	1 (1.2)	0 (0.0)	4 (3.2)
Dyspepsia	3 (3.7)	0 (0.0)	1 (0.8)
Investigations			
ALT increased	3 (3.7)	0 (0.0)	0 (0.0)
Vascular disorders			
Flushing	4 (4.9)	0 (0.0)	1 (0.8)
Renal and urinary disorders			
Polyuria	6 (7.3)	0 (0.0)	1 (0.8)
Nervous system disorders			
Headache	33 (40.2)	4 (15.4)	9 (7.1)
Dizziness	4 (4.9)	1 (3.8)	2 (1.6)

In the **essential hypertension group**, more clevidipine-treated patients had TEAEs (69.5%) than placebo (38.5%). The SOCs with the highest incidence among both clevidipine-treated essential hypertensive patients and placebo patients were nervous system disorders and general disorders and administration site conditions. For clevidipine-treated patients in the essential hypertension group, headache occurred with a notably higher incidence (40.2%) than any other AE; this was followed by infusion site reaction, nausea, and polyuria (7.3% each). In the placebo group, headache and infusion site reaction were the TEAEs with the highest incidence occurring in 15.4% of patients (Table 26). The incidence of treatment-related TEAEs in patients treated with clevidipine for essential hypertension (51.2%) was higher than for patients in any other type of hypertension. For clevidipine-treated patients in the essential hypertension group, headache occurred with a notably higher incidence (36.6%) than any other treatment-related TEAE; this was followed by nausea (7.3%) and polyuria

(6.1%). In the placebo group, headache (15.4%) was the only treatment-related TEAE that occurred in more than one patient.

In the **Phase III studies**, the incidence of TEAEs in the perioperative studies was 95.5% in the clevidipine group and 100% in the all active comparators group; the incidence was lower in the severe hypertension patient population (47.6%). The high rate of AEs observed in the perioperative studies were likely related to the surgical procedure and comorbidities. In the ECLIPSE studies, the incidence of TEAEs with onset during the overall study drug treatment period and up to 1 hour post the termination of study drug was 38.6% in the clevidipine group and 40.3% in the all active comparators group and no event was greater than 2% more common on clevidipine than on the average of all comparators (Table 27)**.** In the Phase III perioperative studies, treatment-related TEAEs were reported for 14.1% of the clevidipine group compared with 9.4% of the all active comparators group. The incidence of treatment-related TEAEs was 9.5% in clevidipine-treated patients in the severe hypertension group.

In the Phase III perioperative hypertension studies, the most common (≥5% for clevidipine) TEAEs with the highest incidence in patients treated with clevidipine were incision site complications (50.8%), atelectasis (40.6%), and atrial fibrillation (32.8%); similar incidences of these events were reported in the all active comparators group of these studies.

In the ECLIPSE studies, common TEAEs observed with clevidipine were sinus tachycardia, nausea, and hypotension.

The most common adverse events observed in clevidipine-treated patients with severe or essential hypertension are consistent with expectations based on class of drug and mode of action. The common TEAEs observed with clevidipine were headache, dizziness, flushing, nausea, vomiting, and polyuria, and are similar to those observed with other vasoactive agents and/or dihydropyridine calcium channel blockers. Many AEs were reported in the perioperative studies and majority of these were consistent with surgical procedures and complications.

Relationship between AEs and rate/ duration of clevidipine infusion

No relationship was observed between the incidence of the most common (≥5%) TEAEs in hypertensive patients and the average infusion rate of clevidipine. While there was an apparent trend of increased incidence of pyrexia (9.1% to 19.1%) across the five infusion rate categories (0 to ≤2, >2 to ≤4, >4 to ≤8, >8 to ≤16, and >16 mg/h), there was an apparent trend of decreased incidence across the five categories for ventricular tachycardia (11.6% to 1.5%), pericardial rub (6.0% to 0%), dyspnoea (8.6% to 1.5%), wheezing (6.9% to 4.4%), urine output decrease (6.5% to 4.4%) and dizziness (8.6% to 2.9%). However, the incidence rates observed in the >16mg/h group are likely to have been influenced by the small numbers of patients (n=68).

Table 27: Most Common (≥10% for clevidipine) Treatment Emergent Adverse Events from Phase III ECLIPSE Studies

System Organ Class **Preferred Term**	**Perioperative Hypertension**	
	Clevidipine (N=752)	**Active Comparators (N=754)**
Cardiac disorders		
Atrial fibrillation	264 (35.1)	248 (32.9)
Sinus tachycardia	220 (29.3)	230 (30.5)
Ventricular extrasystoles	101 (13.4)	96 (12.7)
Ventricular tachycardia	85 (11.3)	72 (9.5)
Respiratory, thoracic and mediastinal disorders		
Atelectasis	347 (46.1)	314 (41.6)
Pleural effusion	236 (31.4)	254 (33.7)
Breath sounds decreased	94 (12.5)	100 (13.3)
Rhonchi	78 (10.4)	78 (10.3)
Injury. Poisoning and procedural complications		
Infusion site complication	436 (58.0)	433 (57.4)
Post procedural pain	119 (15.8)	113 (15.0)
General disorders and administrative site conditions		
Oedema peripheral	124 (16.5)	107 (14.2)
Pyrexia	110 (14.6)	116 (15.4)
Oedema	93 (12.4)	98 (13.0)
Asthenia	97 (12.9)	98 (13.0)
Anasarca	97 (12.9)	92 (12.2)
Pain	89 (11.8)	83 (11.0)
Gastrointestinal disorders		
Nausea	241 (32.0)	241 (32.0)
Constipation	129 (17.2)	136 (18.0)
Vomiting	77 (10.2)	79 (10.5)
Investigations		
White blood cell count decreased	139 (18.5)	125 (16.6)
Haematocrit decreased	120 (16.0)	113 (15.0)
Haemoglobin decreased	108 (14.4)	104 (13.8)
Platelet count decreased	88 (11.7)	71 (9.4)
Body temperature decreased	86 (11.4)	84 (11.1)
Blood calcium decreased	79 (10.5)	69 (9.2)
Psychiatric disorders		

Anxiety	106 (14.1)	94 (12.5)
Confusional state	92 (12.2)	70 (9.3)
Agitation	77 (10.2)	67 (8.9)
Blood and lymphatic system disorders		
Anaemia	208 (27.7)	238 (31.6)
Thrombocytopenia	76 (10.1)	87 (11.5)
Metabolism and nutrition disorders		
Hyperglycaemia	112 (14.9)	120 (15.9)
Vascular disorders		
Hypotension	127 (14.9)	112 (14.9)

No relationship could be determined between the duration of clevidipine infusion (<48 hours, ≥48 hours, and ≥ 72 hours) and the incidence of the most common (≥5% for clevidipine) TEAEs due to differences in patient numbers and type of hypertensive patient receiving clevidipine for <48 hours versus≥48 hours. The most common TEAEs in pati ents who received <48 hours of continuous infusion were incision site complication, atelectasis and atrial fibrillation, which is consistent with the higher proportion of perioperative patients in this category. Headache, infusion site bruising, infusion site reaction, infusion site swelling, infusion site erythema, and dyspepsia were reported at an incidence≥5% for clevidipine only in patients with continuous infusion rates≥48 hours.

The low patient numbers and the predominance of patients with essential hypertension from the TMC-CLV-06-01 study in the ≥48 hours and ≥72 hours groups may explain these observations.

AEs of special interest

AEs of special interest included reflex tachycardia, hypotension, hypovolaemia, oedema, and blood-borne infections.

In perioperative hypertension the incidence of patients with AEs of special interest was similar in the clevidipine group (72.5%) and the all active comparators group (75.0%); the lowest incidence was in the placebo group (30.1%). Oedema and atrial fibrillation were the most common AEs of special interest in either the clevidipine or all active comparators groups.

In patients receiving clevidipine for severe hypertension, the incidence of patients with AEs of special interest was much lower (4.8%) than any of the perioperative hypertension treatment groups.

Only one patient (1.2%) receiving clevidipine for essential hypertension experienced an AE of special interest (atrial fibrillation) and none occurred in patients receiving placebo.

When only the Phase III studies were examined, the incidences of AEs of special interest in patients who received clevidipine perioperatively were similar to the all active comparators group. In patients with severe hypertension treated with clevidipine, the incidences of these AEs were much lower compared with patients treated for perioperative hypertension.

Throughout the Phase III development programme, clevidipine use specified strict aseptic technique and a 12-hour in-use time period. Of the 1,219 patients treated with clevidipine,

there was no difference in infection rates reported as serious compared to placebo or active comparators in the perioperative setting (2.7% clevidipine vs. 3.8% placebo/comparator)

Deaths, SAEs and discontinuations due to AEs

Deaths

There was one death in a clevidipine-treated patient in Phase II studies in hypertensive patients. In Phase III studies of hypertensive patients, the incidence of death was consistent with expectations based on the risk characteristics of the patient populations studied in all treatment groups. Similar mortality rates were observed in clevidipine and active comparator-treated patients in the perioperative ECLIPSE trials.

The three deaths that occurred during the VELOCITY study of severe hypertension occurred in patients who presented with end-stage organ failure, and resulted from continued deterioration in clinical condition despite intensive medical intervention.

Review of death narratives suggested that causes of death were typical of complications known to occur during or following cardiac surgery, or reflected the natural history of advanced severe end organ injury and were unlikely to be related to clevidipine.

SAEs

The incidence and type of SAEs observed in patients who received clevidipine was comparable with what was expected in the perioperative and severe hypertension populations of patients studied. There were no SAEs in essential hypertension patients. There were no clinically relevant differences between clevidipine, placebo, and all active comparators treatment groups with respect to the incidence of SAEs categorised by SOC in hypertensive patients. The incidence of patients with SAEs in patients treated for perioperative hypertension was similar for the clevidipine group (20.3%) and all active comparators group (21.8%), but lower for patients receiving placebo (15.8%). The SOCs with the highest incidence of SAEs were cardiac disorders and respiratory, thoracic, and mediastinal disorders for patients in all treatment groups.

The overall incidence of patients with SAEs in clevidipine-treated patients with severe hypertension (9.5%) was lower than the perioperative hypertension patients in all of the treatment groups. The SOCs with the highest incidences were nervous system disorders and respiratory, thoracic, and mediastinal disorders. In the Phase III studies, the incidence of SAEs in the perioperative patients who received clevidipine (21.1%) was similar to the all active comparators group (22.7%), and higher than the severe hypertension group treated with clevidipine (9.5%) The SOCs were the same as described in the by “type of hypertension” subsection above. The higher incidence of SAEs in perioperative patients suggests some of the SAEs were related to the surgical procedure and other comorbidities.

Discontinuations due to AEs

The incidence of patients with adverse events leading to study drug discontinuation was low (< 6%) in all treatment groups. The incidence of patients with AEs leading to study drug discontinuation in patients with perioperative hypertension receiving clevidipine was 5.9% compared to 3.2% in the combined group treated with active comparator agents. Only one placebo patient discontinued study drug due to an AE (hypertension). Hypotension and hypertension were the most common AEs leading to study discontinuation. However, 17 of the 36 clevidipine-treated patients with AEs (hypotension or hypertension) leading to

discontinuation came from study SAD-0003[*], which was a Phase II dose-finding study conducted in postoperative cardiac surgery patients.

There were six (4.8%) patients treated with clevidipine for severe hypertension discontinued due to AEs with vascular disorders, cardiac disorders, investigations and general disorders and administration site conditions being most common. The incidence of AEs leading to study drug discontinuation was similar in patients treated with clevidipine for severe hypertension (4.8%) compared to patients treated for perioperative hypertension.

In essential hypertension, no placebo patients, but one clevidipine-treated patient discontinued due to AEs in the SOCs of gastrointestinal disorders and nervous system disorders.

In the Phase III studies the incidence of AEs leading to study drug discontinuation for perioperative hypertension patients treated with clevidipine was 4.2% compared with 2.8% in patients treated with all active comparators.

Laboratory parameters

Clevidipine treatment was not associated with any clinically relevant changes in laboratory parameters.

For essential hypertension and perioperative hypertension studies, no clinically significant differences were observed in laboratory data between clevidipine-treated patients and comparators.

Observed increases in triglyceride concentrations with longer infusions of clevidipine were transient and were not associated with clinical sequelae. Median percent increases in blood triglyceride concentrations from baseline to Day 7/last assessment after clevidipine was discontinued were small (11.9% in essential hypertension group and 7.1% in severe hypertension group), and clinically insignificant. The median percent change from baseline in the perioperative group was -8.6%.

The severe hypertension group received longer infusions of clevidipine (median duration 20.7 hours) compared to the perioperative group (median duration on drug of 3 hours). As noted in the clinical study report for VELOCITY, the median percent change in triglyceride values at 6 hours post infusion compared to baseline was zero, indicating that triglyceride concentrations were minimally affected soon after the clevidipine infusion was discontinued.

When evaluating changes in post-infusion triglyceride concentrations, the median percent change from baseline to worst post-infusion value and the median change from baseline to post-infusion values at Day 7/last assessment were both 0% for the severe hypertensive group; for the perioperative hypertension group, there was a change of -8.6% at the worst post-infusion time point and a change of -10.0% at the Day 7/last assessment time point.

The formulation of clevidipine and the dosage typically used to treat essential, perioperative or severe hypertension suggests that clevidipine carries a low potential to cause hypertriglyceridaemia. When clevidipine is given at an infusion rate of 16 mg/h, the patient receives 32 mL/h of intravenous fat emulsions. The fat content of the formulation is 0.2 g/mL, resulting in a fat administration rate of 6.4 g/h, such that a 70-kg individual receiving clevidipine at a rate of 16 mg/h for a period of 24 hours would receive fat at a rate of 0.09 g/kg/h and a dose of 2.2 g/kg/day.

[*] Patients were force-titrated to different dose levels and withdrawn if certain protocol pre-specified BP criteria were met. These withdrawals from treatment were recorded as AEs in this study, thereby influencing this analysis.

Patients on other lipid-based therapies

Critically ill or septic patients and those on corticosteroids, propofol, or parenteral nutrition may be susceptible to the development of hypertriglyceridaemia. In such patients, it is prudent to obtain a baseline serum triglyceride concentration before administering a lipid-based agent such as clevidipine and to monitor triglycerides periodically during therapy.

In perioperative hypertension patients, the median percent increase from baseline to Day 7/last assessment in serum creatinine in clevidipine-treated patients was 0% in all treatment groups. Small increases in serum creatinine were observed in the essential hypertensive studies (both clevidipine-treated and placebo) and the severe hypertension study.

Summary of safety

Clevidipine was well tolerated over the proposed dosage range of 2 mg/h to 32 mg/h in hypertensive patients (including essential, perioperative and severe hypertension) for the proposed duration of up to 72 hours.

Clevidipine-treated patients had a low incidence and severity of hypotension. The incidence of hypotension leading to discontinuation was low (<2%) supporting the safety of the starting dose and dosing regimen.

The incidence of death, MI, stroke and renal dysfunction in perioperative cardiac surgical patients treated with clevidipine was consistent with those expected in this population and similar to comparators.

Following termination of infusion, patients treated with clevidipine did not experience rebound hypertension.

The reflex increase in HR observed in association with clevidipine treatment was similar in magnitude to comparators.

The incidence of observed AEs did not increase with increased drug exposure, with the exception of headache which is a common effect of calcium channel antagonist class. Adverse events and changes in laboratory values were consistent with those expected in these populations and similar in frequency to comparators.

In all patients treated with clevidipine, observed increases in triglyceride concentrations from baseline were transient, independent of type of hypertension, and were not associated with clinical sequelae.

Clevidipine and its major metabolite, H 152/81, were not associated with prolongation of cardiac repolarisation.

Clinical Summary and Conclusions

The efficacy of clevidipine has been consistently established in all studies in a broad population comprising healthy volunteers, patients with preoperative, postoperative, essential and severe hypertension, as well as patient subgroups with a range of comorbidities. Clevidipine lowers blood pressure with rapid onset (within 2 minutes and time to achieve target was 6-10 minutes) and rapid offset (full recovery in 5-15 minutes). The majority of patients achieved target BP with doses <16mg/h, although patients with severe hypertension may benefit with clevidipine doses up to 32mg/h (although experience at this dose rate was limited). There was no evidence of tolerance following clevidipine infusions up to 72 hours.

Evidence from the Phase III ECLIPSE studies in over 1500 cardiac surgery patients with perioperative hypertension demonstrated a significant improvement in BP control achieved in patients managed with clevidipine compared to two commonly used agents in that setting

(glyceryltrinitrate and sodium nitroprusside); however, these results should be interpreted with caution as efficacy was a secondary endpoint and non-inferiority margins were not pre-specified.

Safety and tolerability have been examined in a large database of patients representative of those expected to receive clevidipine in marketed use and encompassing the three different presentations of hypertension (essential, perioperative and severe). The safety of the starting dose was confirmed by a low incidence of hypotension. Clevidipine was safe and well tolerated over the proposed dosage range of 2 mg/h to 32 mg/h for the proposed duration of up to 72 hours. The patterns of adverse events (AEs) observed in patients with perioperative and severe hypertension were consistent with those expected for these patient populations. There are no patterns suggesting an increase in any category of AE in clevidipine-treated patients compared to the relevant control groups and no apparent differences in patients with comorbidities (or other potentially important covariates). There were also no issues observed in relation to the lipid formulation, method of administration or BP monitoring. There is no evidence of drug accumulation, tolerance, or rebound hypertension and the rapid offset is independent of duration of infusion.

Clevidipine's pharmacokinetic profile of rapid metabolism to inactive metabolites and non-dependence on liver or renal function for its metabolism or elimination contributes to its safety. There is no requirement for weight-based dosing.

Currently there are no consensus guidelines or treatment protocols for the control of acute hypertension using intravenous (IV) therapies; consequently, treatment options vary worldwide. Nicardipine, a dihydropyridine antihypertensive is approved in the USA for short-term treatment of hypertension, when oral therapy is not feasible or desirable. Clevidipine and nicardipine appeared to show similar efficacy in the ECLIPSE study, although non-inferiority margins were not pre-defined. However, the main features differentiating clevidipine are its metabolism and pharmacokinetics. Clevidipine is metabolised by plasma and tissue esterases. No dose adjustment is needed for patients with hepatic or renal impairment and there is little likelihood of drug interactions. Clevidipine is arterial selective and has little effect on venous haemodynamics. Furthermore, Clevidipine has been consistently effective and well tolerated and would provide an important therapeutic option for short-term treatment of hypertension, when oral therapy is not feasible or desirable.

Recommendation:

The evaluators recommended that Cleviprex be approved for the short-term treatment of hypertension, when oral therapy is not feasible or desirable. This will usually be in a hospital setting and thus the indication should state "Use is in Hospital Setting Only

V. Pharmacovigilance Findings

Risk Management Plan

The sponsors submitted a risk management plan for Cleviprex as agreed in the pre-submission meeting with the TGA. The routine pharmacovigilance and other measures to address specific safety concerns associated with clevidipine are outlined in Table 30. These appear to adequately address safety concerns associated with use of clevidipine, including monitoring to address lack of information regarding risks in certain patient populations (pregnancy/ lactation and paediatric populations).

Table 28: Summary of safety Concerns and Planned Pharmacovigilance Activities

Safety Concern	Planned Actions
Important Identified Risks	
Unwanted hypotension or 'overshoot' hypotension	Active surveillance of hypotension events including the use of targeted questions in the receipt and follow-up of adverse events to ensure high quality and complete information
Reflex tachycardia	Inclusion of discussion of hypotension, reflex tachycardia and events associated with lipid overload in the Periodic Safety Update Report (PSUR)
Important Potential Risks	
Nosocomial or hospital-acquired infections	Active surveillance of events of infection including the use of targeted questions in the receipt and follow-up of adverse events of the infection to ensure high quality and complete information
Lipid overload	Inclusion of discussion of reports describing nosocomial or hospital-acquired infections and events associated with lipid overload in the PSUR
	Nosocomial or hospital-acquired infections will be defined by MedDRA preferred terms and will be reviewed on a monthly basis
Important missing information	
Exposure to clevidipine during pregnancy and lactation	Ongoing AE report surveillance for pregnant and lactating patients
Use of clevidipine in the paediatric population	Ongoing AE report surveillance for indicators and clinical circumstances of AEs in paediatric patients

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval was recommended from a chemistry, quality control and bioavailability aspect. Cleviprex is a racemic mixture of two enantiomers that are related to other dihydropyridines and in particular felodipine. Clevidipine has a low solubility and therefore the product is presented as an oil-in-water emulsion with the drug substance dissolved in the oil droplets. The product is a sterile injection that shows a decrease in assay and pH and an increase in related substances on storage but within acceptable expiry limits. Acceptable limits were found for endotoxins, sterility, subdivisible particulate matter and droplet size. The degradation of phosphatidyl choline, which is present in egg lecithin, to lysophosphatidyl choline has been associated with haemolytic anaemia but an acceptable limit has been agreed. The product is not to be mixed with other medications in the same administration line. No absolute bioavailability studies were conducted since the product is administered by the intravenous route. The PSC of ADEC had no objections to registration and the product has a shelf life of 26 months at 2-8°C.

Nonclinical

The non-clinical evaluator raised no objections to registration. Pharmacology studies showed a lack of significant detrimental effects and rapid reversal of antihypertensive action. Pharmacokinetic studies showed linear pharmacokinetics, rapid attainment of steady state in 2-5 minutes, high protein binding, extensive extra-hepatic clearance, rapid conversion to an inactive metabolite and an unlikeliness to induce CYP activity or inhibit drug metabolism via CYP given only CYP3A4 showed a modest induction by clevidipine. Repeat dose toxicity studies used exposure ratios in rats that were similar to humans but in dogs used exposure ratios that were 3-4 times greater with most changes seen attributable to vehicle or surgery effects. Genotoxicity was positive *in vitro*, but not *in vivo*, which was consistent with the formation of formaldehyde, a probable human carcinogen. However this exposure to formaldehyde in humans is several hundred times less than normal daily exposure from endogenous formaldehyde generation. Other prodrugs with similar levels of formaldehyde generation have been registered (for example, adefovir, fosphenytoin). Therefore genotoxicity was determined to not be of clinical concern. No long term carcinogenicity studies are available given the short term use of the product. Clevidipine did not cause significant effects on fertility but did slow rat fetal development but no teratogenicity. At doses similar to human doses, there was decreased rat and rabbit fetal survival during organogenesis and increases in maternal mortality, length of gestation and prolonged parturition at doses 1/6 of human doses when administered during late gestation and parturition, which probably reflects drug induced inhibition of uterine contractions (calcium channel blocker class effect, Pregnancy Category C).

Clinical

Pharmacology

The clinical evaluator noted the following effects of clevidipine:

- Clevidipine demonstrates a rapid onset of action (2-10 min) in all hypertensive patients. Following a 20 minute constant infusion of clevidipine (3.2 μg/min/kg; 16 mg/h) in healthy volunteers, the time to onset of effect was less than 5 minutes from the start of clevidipine infusion to the attainment of maximal effect on haemodynamic parameters. Similarly, in patients with mild to moderate hypertension (TMC-CLV-06-01), administration of clevidipine (2.0, 4.0, 8.0 and 16.0 mg/h) for 72 hours led to rapid onset of drug effect (3%-18% decrease in SBP from baseline within 10 minutes) for all dose cohorts followed by a rapid return (within 10 minutes) to baseline SBP on cessation of treatment. In study TMC-CLV-06-02, clevidipine was administered to patients with severe hypertension for up to 60 hours and the SBP was successfully decreased to the initial pre-specified SBP target range within 30 minutes of initiation of clevidipine infusion (median time 10.9 minutes).
- The time to recovery of the haemodynamic effect is short, and in most studies the SBP, MAP and HR return to baseline values within minutes after discontinuation of clevidipine
- The therapeutic dose-rate range for clevidipine suitable for a clinical setting ranged from 0.18 to 3.19 μg/kg/min (0.9 mg/h to 15.3 mg/h) (study SAD-0003).
- The mean dose rate required to control BP during pre-bypass (2.17 μg/kg/min or 11 mg/h) was higher than that required to control BP during bypass (1.26 μg/kg/min or 6 mg/h), which was most likely due to reduced clevidipine clearance during bypass hypothermia (study SAD-0006).

- There is a correlation between the arterial blood concentrations and dynamic response during and after the short infusion of clevidipine. This correlation between concentration and response, taken together with the rapid clearance of this agent suggest that clevidipine can be rapidly titrated to the desired effect (study SAD-0018).
- Clevidipine rapidly reduced MAP and induced a systemic, pulmonary and coronary vasodilation with no effect on venous capacitance vessels or HR. Cardiac output and stroke volume increased by 10%. Results of study SAD-0005 suggested a dose-dependent vasodilatory effect on coronary vessels with no negative effect on myocardial lactate metabolism.

Pharmacokinetics

The clinical evaluator noted the following effects of clevidipine from the pharmacokinetic studies:

- The same drug product formulation has been used consistently across the clinical development program, thus relative bioavailability or bioequivalence studies were not required.
- The pharmacokinetics of clevidipine is linearly related to the dose. At dose rates of 0.3 to 3.2 µg/kg/min, the steady state plasma concentrations for clevidipine are 10 to 100 nmol/L (4.57 to 45.7 µg/L), respectively.
- Clevidipine concentrations in arterial blood are twofold higher than those in venous blood during continuous infusion. The time to reach steady-state venous blood concentration of clevidipine is less than 5 minutes (2 minutes in arterial blood).
- Length of infusion has no effect on the kinetics of clevidipine for infusions of up to 72 hours.
- Blood concentrations decline in a multi-phase pattern following termination of the infusion. The alpha phase half-life is approximately 1 minute, and accounts for 85% to 90% of clevidipine elimination. The terminal half-life is approximately 15 minutes.
- Rapid metabolism by esterases in the blood and extravascular tissues, to an inactive metabolite which is excreted in the urine and faeces. Elimination is therefore largely independent of liver and renal function.
- Pharmacokinetic parameters were similar in healthy volunteers, patients with essential hypertension and patients with peri-operative hypertension.
- Clevidipine and its primary metabolite do not induce or inhibit cytochrome P450 isoenzymes at clinically relevant concentrations. The concentration of clevidipine and its major metabolite inducing/ inhibiting some of the P450 isoforms were at least 10 times higher than the highest clevidipine concentration typically seen in the clinic (16 mg/h at 100 nmol/L). In addition, the magnitude of induction/inhibition was much less than the positive control.
- No clinical drug interaction studies were conducted, but it appears to be unlikely for clevidipine and its major metabolite to cause cytochrome P450 related drug interactions when used in the dose range required to manage hypertension in man. Clevidipine elimination was not significantly affected by the majority of simultaneously administered drugs (sodium thiopental, fentanyl, morphine, isoflurane, diltiazem and propofol showed no effect on the hydrolysis of clevidipine to its major inactive metabolite but

pancuronium and vecuronium reduced the hydrolysis by 26-28%) or by the deficiency of pseudocholinesterase in some patients.

- Anaesthesia does not affect the clearance of clevidipine. Systemic arterial clearance of clevidipine is 5 L/min in healthy volunteers and 4.8 L/min in anaesthetised normothermic patients. Cardiopulmonary bypass with mild hypothermia and haemodilution reduces the rate of clearance by 50% to approximately 0.03 L/kg/min. However, since clevidipine is titrated to blood pressure lowering effect, any minor differences in clearance in this context would not impact the safety of the dosing regimen due to the individualised patient-specific approach.

Efficacy

Phase II studies in mild to moderate essential hypertension: Three Phase II studies (n=95) demonstrated some evidence of rapid reduction in mean arterial pressure with clevidipine. Trial ***SAD-0004*** using 0.3-3mg/hr produced 5-15% reduction, ***SAD-0010*** showed a rapid reversal of effect and ***TMC-CLV-06-01*** showed tolerance did not develop during continuous infusion of 72 hours and there was no evidence of rebound hypertension following cessation of clevidipine infusion. These studies excluded patients with CHF, arrhythmia, recent MI, recent stroke, angina and valvular disease.

Phase II studies in peri-operative hypertension during cardiac surgery: Six Phase II studies (n=337) were conducted and three of these demonstrated the following: SAD-0003 showed the therapeutic dose range is 0.18 to 3.19ug/mL (0.9 mg/h to 15.3 mg/h), SAD-0006 showed the dose required to control BP during pre-bypass was higher than during bypass and SAD-0005 suggested a dose dependent vasodilatory effect on coronary vessels. These studies excluded patients with poor LVF, recent MI, stroke, renal impairment and hepatic impairment. SAD-0013 (n=30) was a double blind, randomised active controlled parallel study in patients with systolic BP≥145mmHg or mean arterial pressure (MAP) of ≥90mmHg for 3 hours infusion of clevidipine vs. sodium nitroprusside using a titrated dose. The primary efficacy endpoint of number of dose adjustments made to maintain MAP to 70-80mmHg was not different between the two treatments but there was a wide confidence interval and there appeared to be an upward trend to more dose adjustments for clevidipine. SAD-0017 (n=60) was a double blind, randomised, placebo controlled parallel study in patients needing extracorporeal circulation and a variable MAP target. This showed a significantly greater reduction in MAP at 10minutes compared to placebo (-28.2 vs. -10.5mmHg, difference of -17.7mmHg, 95% CI -23.1, -12.3). MAP was better controlled in the clevidipine group and there did not appear to be an effect on heart rate. TMC-CLV-02-01 (n=100) was a double blind, randomised, active controlled parallel study in patients undergoing coronary artery bypass grafting comparing clevidipine (max 40mg/hr) with glyceryltrinitrate for BP control and preservation of renal function from induction of anaesthesia to 12 hrs post-operative. Clevidipine showed non-inferiority compared to glyceryltrinitrate for BP control and was similar for glomerular function and renal tubular function.

Phase III studies in pre- and post-operative hypertension: Five studies were included here with patients having urgent or elective cardiac surgery and broader inclusion criteria with only recent stroke being a significant exclusion criterion.

ESCAPE-1 and ESCAPE-2: These studies were multicentre, randomised double blind, placebo controlled parallel trials in 104 hypertensive pre-operative patients undergoing cardiac surgery (SBP ≥160mmHg) and 110 patients with post-operative hypertension (SBP ≥140mmHg within 4 hours post-op) comparing clevidipine (2mg/hr titrated every 90 seconds

to 16mg/hr or maximum of 40mg/hr) with placebo for 30min to 1 hour (or anaesthesia induction). Baseline characteristics showed a difference in age in ESCAPE-1 (63% >65yo on clevidipine vs. 35% on placebo) and more prior MIs in the clevidipine arm whereas placebo had a higher family history of coronary artery disease. In ESCAPE-2, there were again more patients >65 yo on clevidipine and higher CCF whereas placebo had higher incidence of angina. The primary efficacy endpoint of incidence of bailout (premature and permanent discontinuation due to safety or efficacy reasons) during the 30min evaluation period showed a higher rate of treatment success (absence of bailout) on clevidipine vs. placebo of 92.5% vs. 17.3%, $p<0.0001$ in ESCAPE-1 and 91.8% vs. 20.4%, $p<0.0001$ in ESCAPE-2. The median time to a >15% reduction in SBP was 5.3-6 minutes and the majority used a dose of 16mg/hr or less.

ECLIPSE studies: These three studies were open label, randomised, active controlled trials comparing clevidipine (2mg/hr to >16mg/hr) with glyceryltrinitrate, sodium nitroprusside or nicardipine to primarily assess safety in the peri- and post-operative cardiac surgery setting by comparing incidences of death, stroke, MI and renal dysfunction at day 30 and to assess efficacy as a post-operative secondary endpoint but without hypothesis testing. Patients required treatment for hypertension (no predefined criteria) and were undergoing CABG, bypass or valvular surgery. The baseline characteristics were similar between groups, except more prior CABG in the glyceryltrinitrate arm. Baseline diastolic BP was a mean 69-72mmHg and baseline systolic BP was a mean 141mmHg. Most patients had a history of hypertension. Using $AUC_{SBP\text{-}D}$ (area under the curve for SBP excursions below predefined SBP range normalised per hour) as the efficacy endpoint, clevidipine was better than glyceryltrinitrate in ECLIPSE-NTG (n=546) and significantly better than sodium nitroprusside in ECLIPSE-SNP (n=579) but no difference to nicardipine in ECLIPSE-NIC (n=381).

Phase III study in severe hypertension, TMC-CLV-06-02 (VELOCITY): This is a open label, single group trial in 126 patients with severe hypertension (SBP>180mmHg and DBP >115mmHg) in the ICU, CCU or Emergency Dept. using clevidipine at a dose of 2mg/hr titrated every 3 minutes to maximum of 32mg/hr or as pre-determined for the patient for 18 to 96 hours. The population had 95% history of hypertension, 77% African Americans and 81% end organ damage (left ventricular hypertrophy, renal dysfunction, retinal damage, focal neurological changes). The primary efficacy endpoint of percentage of patients reaching the SBP target range within 30minutes was 89% of patients with a mean decrease of 21% at 30minutes. In those who had continuous 18hr infusion, 92% were managed without additional IV antihypertensives. The change in SBP for those going from 16 to 32mg/h compared to those going from 8 to 16mg/hr was 6.5 mmHg. The time to SBP target range was 10.9minutes and 91% of patients were successfully transitioned to oral antihypertensives within 6 hours of discontinuing clevidipine.

Dose response analysis: The Phase II and III studies examining dose-response confirm that an appropriate starting dose of clevidipine is 2 mg/hr. A linear relationship exists between clevidipine dose, reduction of BP and clevidipine blood concentrations, including a linear relationship between clevidipine dose and percent change in SBP at doses up to 20 mg/hr. However, there is a flattening of the dose-response relationship at doses greater than 20 mg/hr and up to 32 mg/hr. Although, the effective clevidipine dose range is 2 to 32 mg/hr, most patients will achieve the desired therapeutic response at doses≤16 mg/hr and only some patients with severe hypertension may require doses up to 32 mg/hr. The dose-response relationship observed in the combined ESCAPE and VELOCITY studies predicts an approximate reduction in SBP of 1% per 1 mg/hr incremental increase in dose level. Clevidipine infusion administered continuously for up to 72 hours across the entire

therapeutic dose range was not associated with the development of tolerance in TMC-CLV-06-01 and VELOCITY.

Safety

Total exposure to clevidipine was 1307 patients and 99 healthy subjects across 15 studies. Adverse events were assessed for 7 days post drug or 30 days post drug for serious adverse events. Hypertensive patients were exposed for a median 6.4hrs (92% <24hrs) and up to 60mg/hr (80% <8mg/hr). The severe hypertensive patients were exposed for a median 20.7hrs (93% >18hrs). Healthy volunteers were exposed for a median of 1hr and the most common AEs were headache, nausea, dizziness and flushing. An ECG study showed modest effects on QTc of a median change of 5msec and upper 95% confidence interval of <10 msec along with higher heart rates. Clevidipine was well tolerated over the proposed dosage range of 2 mg/h to 32 mg/h in hypertensive patients (including essential, peri-operative and severe hypertension) for the proposed duration of up to 72 hours. Patient baseline characteristics were generally similar across clevidipine, placebo and active comparators but the severe hypertension study had some notable differences (for example, 77% African American).

The ECLIPSE studies which used a primary safety endpoint showed similar results between clevidipine and comparators for the incidences of death, MI, stroke or renal dysfunction at 30 days as expected for this population and no clinically meaningful differences in subgroups.

Clevidipine-treated patients had a low incidence and severity of hypotension (14.5% vs. 15.5% for active comparators). The incidence of hypotension leading to discontinuation was low (<2%) supporting the safety of the starting dose and dosing regimen. Following termination of infusion, patients treated with clevidipine showed similar levels of rebound hypertension to active comparators but greater than placebo for those with >20% increase from baseline BP. The reflex increase in HR observed in association with clevidipine treatment was similar in magnitude to comparators (for example, in peri-operative hypertensive group was 89.5 bpm for placebo, 98 bpm for clevidipine and 102 bpm for all active comparators).

The incidence of observed AEs increased for pyrexia with increasing infusion rate but decreased for ventricular tachycardia, pericardial rub, dyspnoea, wheezing and dizziness. Headache increased with drug exposure, which is a common effect of the calcium channel antagonist class. Adverse events and changes in laboratory values were consistent with those expected in these populations or the surgical settings and similar in frequency to comparators. The common AEs were headache, dizziness, flushing, nausea, vomiting and polyuria. The incidence of treatment emergent adverse events was greater on clevidipine than for all active comparators in the all hypertensive population (19% vs. 10.5%) but similar in the peri-operative population (92% vs. 95%). In the peri-operative setting, common AEs were incision site complications, atelectasis and atrial fibrillation which were similar to the active comparator group. AEs of special interest (reflex tachycardia, hypotension, hypovolaemia, oedema and blood borne infections) were similar between clevidipine and active comparators but lower in the severe hypertension study. In the ESCAPE 1 study, acute renal failure was higher on clevidipine than placebo (9% vs. 2%), and in ESCAPE 2 study, atrial fibrillation and nausea were higher on clevidipine than placebo (21% vs. 12%) and (21% vs. 12%). Mortality rates were similar between clevidipine and active comparators and there were three deaths in the severe hypertension study (all had end stage organ failure). Serious AEs were similar between clevidipine (20%) and active comparators (22%) but greater than placebo (16%) and were greatest for cardiac, respiratory, thoracic and mediastinal disorders. Serious AEs were less in the severe hypertension study (9.5%). AEs leading to study discontinuation was <6% in all groups. Laboratory changes were similar between clevidipine and active

comparators but there were increases in triglycerides which were transient, independent of type of hypertension, and were not associated with clinical sequelae but those on lipid based therapies may need a baseline triglyceride measurement.

Issues

The issues noted by the clinical evaluator included:

- Whether the indication should include "short term" treatment, whether the indication should be described as "treatment of hypertension" vs. "reduction of blood pressure" and whether it should state "use is in hospital setting only".
- Efficacy was a secondary endpoint in the ECLIPSE studies and non-inferiority margins were not defined for the active controlled trials.
- Lack of consensus guidelines or treatment protocols for the treatment of acute hypertension using intravenous therapies.

Risk-Benefit Analysis

Efficacy

Clevidipine has demonstrated efficacy in the two ESCAPE studies against placebo in the setting of pre- and post-operative cardiac surgery hypertension. The studies showed significant reductions in BP although there was some baseline imbalance in patient characteristics. Data has also been submitted in mild to moderate hypertension in the phase II studies and severe hypertension in a phase III study but the latter study lacked a control arm and was open label. The active controlled ECLIPSE studies implied a benefit for clevidipine compared to nitroprusside and glyceryltrinitrate but not nicardipine (calcium channel blocker). However this should be interpreted with caution given the open label design (although a double blind design appears to be impractical due to the lipid emulsion), efficacy as a secondary endpoint, lack of hypothesis testing and lack of non-inferiority margins. The active comparators used in the ECLIPSE studies were also not approved for rapid up-titration. Clevidipine demonstrated rapid onset and offset with most patients achieving target with doses of <16mg/hr but up to 32mg/hr in severe hypertension. There did not appear to be tolerance up to 72 hours.

Safety

Clevidipine appears to be well tolerated with a safety profile similar to active comparators and as expected for this population and the surgical setting. The safety data are limited but indicate a low incidence of hypotension, similar rebound hypertension and reflex tachycardia as comparators, some dose related changes (for example, headache, pyrexia) and the need to consider triglyceride measurement in those receiving other lipid based therapies. The ECLIPSE studies which assessed a primary safety endpoint showed similar results to active comparators, but this lacked formal hypothesis testing. Acute renal failure, atrial fibrillation and nausea were noted to be higher on clevidipine than placebo.

Pharmacology

Clevidipine showed a rapid metabolism to an inactive metabolite and was no dependent on hepatic or renal function for its elimination and therefore should not require dose adjustment in these settings. Weight based dosing did not appear to be required.

Deficiencies

There were no *in vivo* drug interaction studies even though patients would normally be on multiple medications including other antihypertensives but clevidipine is rapidly metabolised to an inactive metabolite by plasma and tissue esterases and drug interactions were deemed unlikely by the evaluator. *In vitro* data indicated some CYP3A4 induction. The ECLIPSE trials had some issues (open label, lack of non-inferiority margins and no hypothesis testing) which makes interpretation of the efficacy data unclear. Nicardipine is not registered in Australia therefore its validity as an active comparator is limited but it is approved in the USA for short term treatment when oral therapy is not feasible or desirable. There were no studies in other surgical settings or with multiple other medications. The study in severe hypertension lacked a control arm and blood pressure target was sometimes set per-patient rather than a population predefined target. The evidence for maximum duration of treatment and maximum dose are limited but appear to be about 72 hours and 32mg/hr respectively. There is a lack of robust clinical outcome data and a lack of data on patients normalising blood pressure.

Short term use

The clinical evaluator has recommended the indication include "short term" since the pivotal placebo controlled studies, ESCAPE 1 and 2, assessed efficacy over 30 minutes. The sponsor has indicated its preference for including the duration of use in the Dosage section of the PI by stating treatment duration may vary for each patient, including the mean duration from the phase 3 trials and noting little experience beyond 72 hours.

Reduction of blood pressure

The clinical evaluator has recommended the indication be for the treatment of hypertension rather than reduction of blood pressure since the clinical studies were in patients who had essential, severe and peri-operative hypertension. The sponsor has indicated its preference for "reduction of blood pressure" since "hypertension" suggests all patients must present with elevated systolic or diastolic blood pressure whilst "reduction of blood pressure" characterises the physiological effects of clevidipine and the ECLIPSE studies used patients who were not necessarily hypertensive (systolic BP 141±24mmHg).

Overall, the data appear sufficient to support short term use for reducing blood pressure in hypertensive patients when oral therapy cannot be used. The Delegate proposed to approve the submission for the following indication:

short term treatment of hypertension when oral therapy is not feasible or desirable.

The sponsor should address the following issue in their Pre-ADEC response:

- The clinical evaluator's recommendation for measuring triglycerides in those receiving lipid based therapies and any proposed changes to the PI.

The Delegate also requested the advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) on the following two issues:

- Should the indication state "short term" use or can this be included in the Dosage section of the PI?
- Should the indication refer to the "treatment of hypertension" or the "reduction of blood pressure"?

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval with the following indication:

for the short term treatment of hypertension when oral therapy is not feasible or desirable

In making this recommendation, ACPM agreed with the Delegate that the quality, safety and efficacy have been satisfactorily demonstrated. Additionally, the Committee agreed that the term 'hypertension' is being used appropriately and that the indication should refer to short term use. However, the Committee raised the concern that drug interaction data were not available for Cleviprex.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cleviprex containing clevidipine butyrate solution for injection 25 mg in 50 mL and 50 mg in 100 mL for the indication:

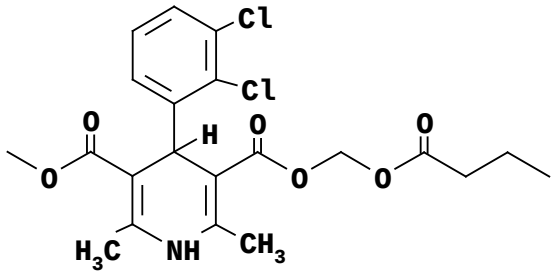
the short term treatment of hypertension when oral therapy is not feasible or desirable.

Attachment 1. Product Information

CLEVIPREX
Product Information

NAME OF THE MEDICINE

CLEVIPREX 0.5mg/mL injection vial. Each mL contains 0.5mg of clevidipine butyrate.



CAS number: 167221-71-8

DESCRIPTION

Chemical name: 3-O-(butanoyloxymethyl) 5-O-methyl-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Molecular formula: $C_{21}H_{23}Cl_2NO_6$ MW: 456.3

Clevidipine butyrate is a white to off-white powder. It is practically insoluble in water.

Cleviprex is a sterile, milky-white opaque emulsion containing 0.5 mg/mL of clevidipine butyrate, soya oil, glycerol, lecithin-egg and sodium hydroxide to adjust pH. Cleviprex has a pH of 6.0 – 8.8 and is a ready-to-use emulsion.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Clevidipine butyrate is a dihydropyridine L-type calcium channel blocker. L-type calcium channels mediate the influx of calcium during depolarisation in arterial smooth muscle. Experiments in anaesthetised rats and dogs show that clevidipine butyrate reduces mean arterial blood pressure by decreasing systemic vascular resistance. Clevidipine butyrate does not reduce cardiac filling pressure (pre-load), confirming lack of effects on the venous capacitance vessels.

Pharmacodynamic effects

Cleviprex is titrated to achieve the desired reduction in blood pressure. In the perioperative patient population, Cleviprex produces a 4-5% reduction in systolic blood pressure (SBP)

within 2-4 minutes after starting a 0.4 mcg/kg/min infusion (approximately 1-2 mg/h). In studies of up to 72 hours there was no evidence of tolerance.

In most patients, full recovery of blood pressure is achieved in 5-15 minutes after the infusion is stopped. In studies of up to 72 hours there was no evidence of rebound hypertension.

Haemodynamics
Cleviprex causes a dose-dependent decrease in systemic vascular resistance.

A reflex increase in heart rate may be a normal response to vasodilation and decreases in blood pressure, the observed effect being similar for clevidipine and all other comparators studied; in some patients these increases in heart rate may be pronounced (see PRECAUTIONS)

The effect of Cleviprex in anaesthetised cardiac surgery patients on central haemodynamics, myocardial blood flow and metabolism was studied. In these patients, cardiac output and stroke volume increased by 10%. As the dose of Cleviprex was escalated, myocardial oxygen extraction decreased significantly, indicating preservation of myocardial perfusion and a direct coronary vasodilatory effect. No increase in net lactate production in coronary sinus blood was observed, confirming the absence of myocardial ischaemia due to coronary steal.

Pharmacokinetics

Clevidipine butyrate is rapidly distributed and metabolised, resulting in a very short half-life. The arterial blood concentration of clevidipine butyrate declines in a multiphasic pattern following termination of the infusion. The initial phase half-life is approximately 1 minute, and accounts for 85-90% of clevidipine butyrate elimination. The terminal half-life is approximately 15 minutes.

Distribution*:* Clevidipine butyrate is >99.5% bound to proteins in plasma at 37°C. The steady state volume of distribution was determined to be 0.17 L/kg in arterial blood.

Metabolism and Elimination*:* Clevidipine butyrate is rapidly metabolised by hydrolysis of the ester linkage, primarily by esterases in the blood and extravascular tissues, making its elimination unlikely to be affected by hepatic or renal dysfunction. The primary metabolite is the carboxylic acid metabolite and formaldehyde formed by hydrolysis of the ester group. The carboxylic acid metabolite is inactive as an antihypertensive. This metabolite is further metabolised by glucuronidation or oxidation to the corresponding pyridine derivative. The clearance of the primary dihydropyridine metabolite is 0.03 L/h/kg and the terminal half-life is approximately 9 hours.

In vitro studies showed that clevidipine butyrate and its metabolite did not markedly inhibit or induce CYP enzymes at the concentrations achieved in clinical practice.

In a clinical study with radio-labelled clevidipine butyrate, 83% of the drug was excreted in urine and faeces. The major fraction, 63-74% is excreted in the urine, 7-22% in the faeces. More than 90% of the recovered radioactivity is excreted within the first 72 hours of collection.

CLINICAL TRIALS

Perioperative Hypertension

Cleviprex was evaluated in two double-blind, randomized, parallel, placebo-controlled, multicenter trials in cardiac surgery patients undergoing coronary artery bypass grafting, with or without valve replacement. Pre-operative use was studied in ESCAPE-1 (n=105); post-operative use in ESCAPE-2 (n=110). Inclusion in ESCAPE-1 required a systolic pressure ≥160 mmHg. In ESCAPE-2, the entry criterion was systolic pressure of ≥140 mmHg within 4 hours of the completed surgery. The mean baseline blood pressure was 178/77 mmHg in ESCAPE-1 and 150/71 mmHg in ESCAPE-2. The population of both studies included 27% females, 47% of patients were older than age 65.

Cleviprex was infused in ESCAPE-1 preoperatively for 30 minutes, until treatment failure, or until induction of anaesthesia, whichever came first. Cleviprex was infused in ESCAPE-2 postoperatively for a minimum of 30 minutes unless alternative therapy was required. The maximum infusion time allowed in the ESCAPE studies was 60 minutes.

In both studies infusion of Cleviprex was started at a dose of 1-2 mg/hour and was titrated upwards, as tolerated, in doubling increments every 90 seconds up to an infusion rate of 16 mg/hour in order to achieve the desired blood pressure-lowering effect. At doses above 16 mg/hour increments were 7 mg/hour. The average Cleviprex infusion rate in ESCAPE-1 was 15.3 mg/hour and in ESCAPE-2 it was 5.1 mg/hour. The mean duration of exposure in the same ESCAPE studies was 30 minutes for the Cleviprex- treated patients.

Approximately 4% of Cleviprex-treated subjects in ESCAPE-1 and 41% in ESCAPE-2 were on concomitant vasodilators during the first 30 minutes of Cleviprex administration.

Cleviprex lowered blood pressure within 2-4 minutes. The change in systolic blood pressure over 30 minutes for ESCAPE-1 (preoperative) and ESCAPE-2 (postoperative) are shown in Figure 1 and 2.

Figure 1. Mean change in systolic blood pressure (mmHg) during 30-minute infusion, ESCAPE-1 (preoperative)

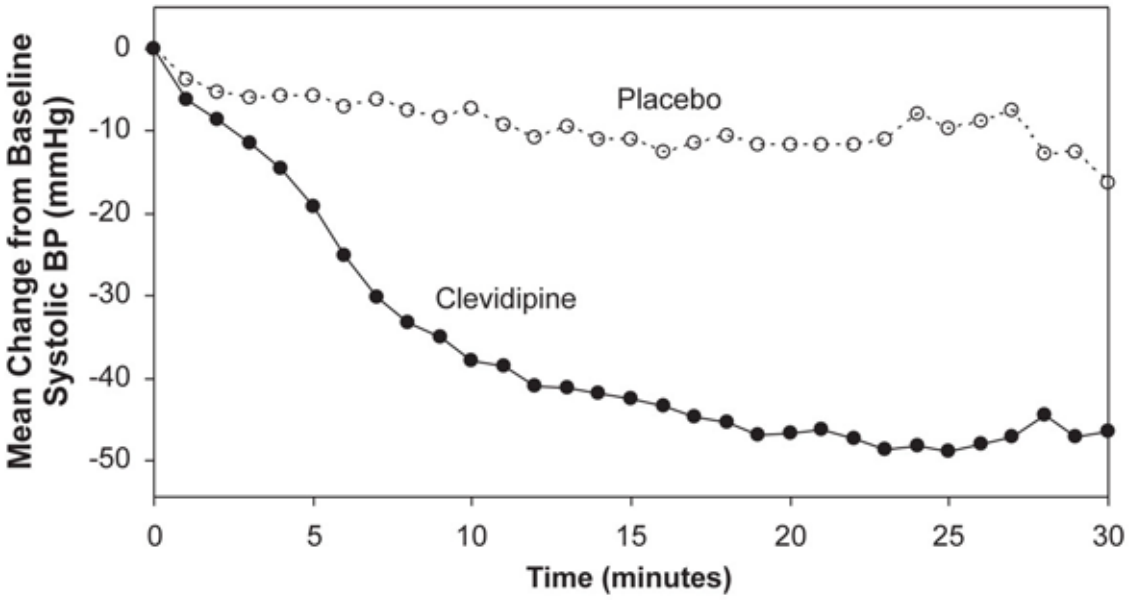
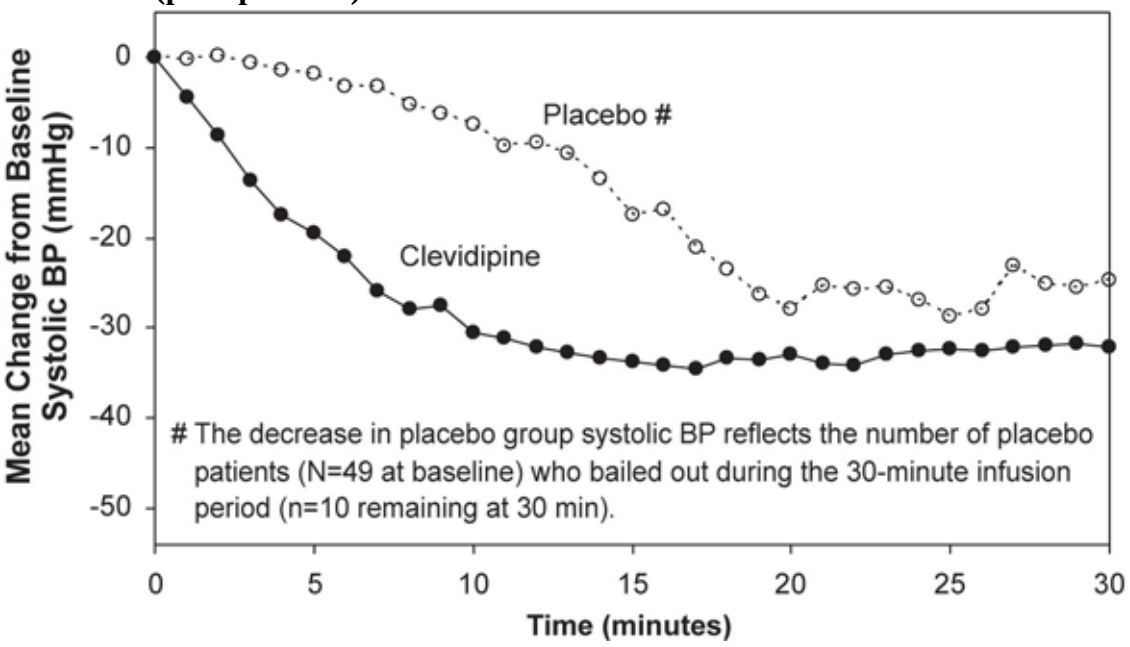


Figure 2. Mean change in systolic blood pressure (mmHg) during 30-minute infusion, ESCAPE-2 (postoperative)



The change in heart rate over 30 minutes for ESCAPE-1 (preoperative) and ESCAPE-2 (postoperative) are shown in Figure 3 and 4.

Figure 3. Mean change in heart rate (bpm) during 30-minute infusion, ESCAPE-1 (preoperative)

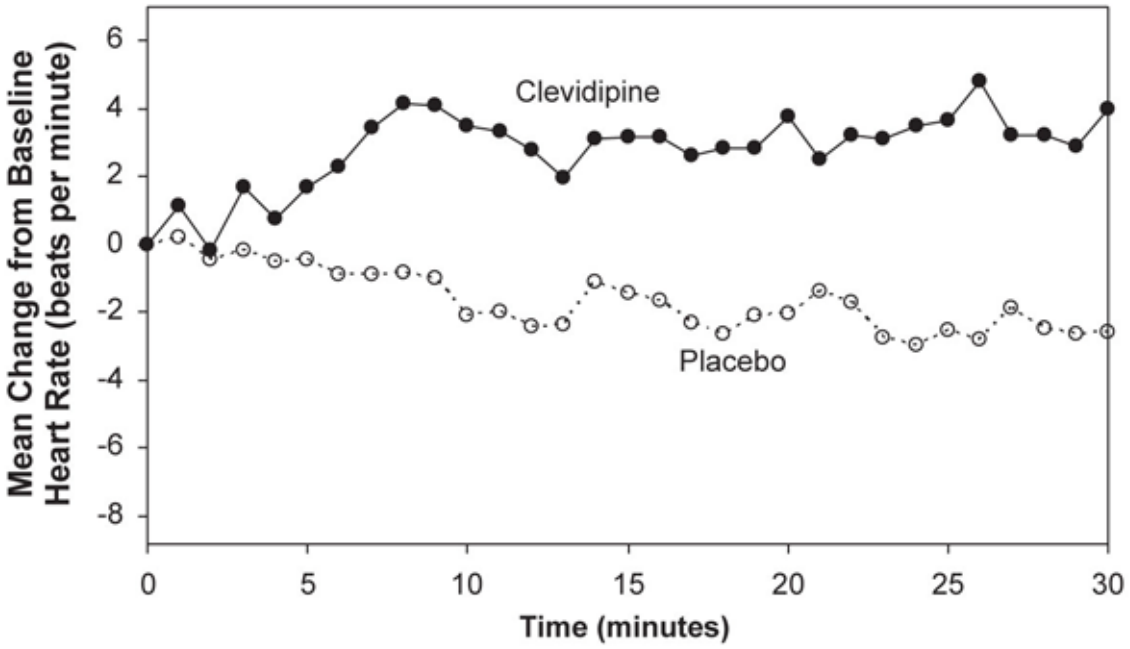
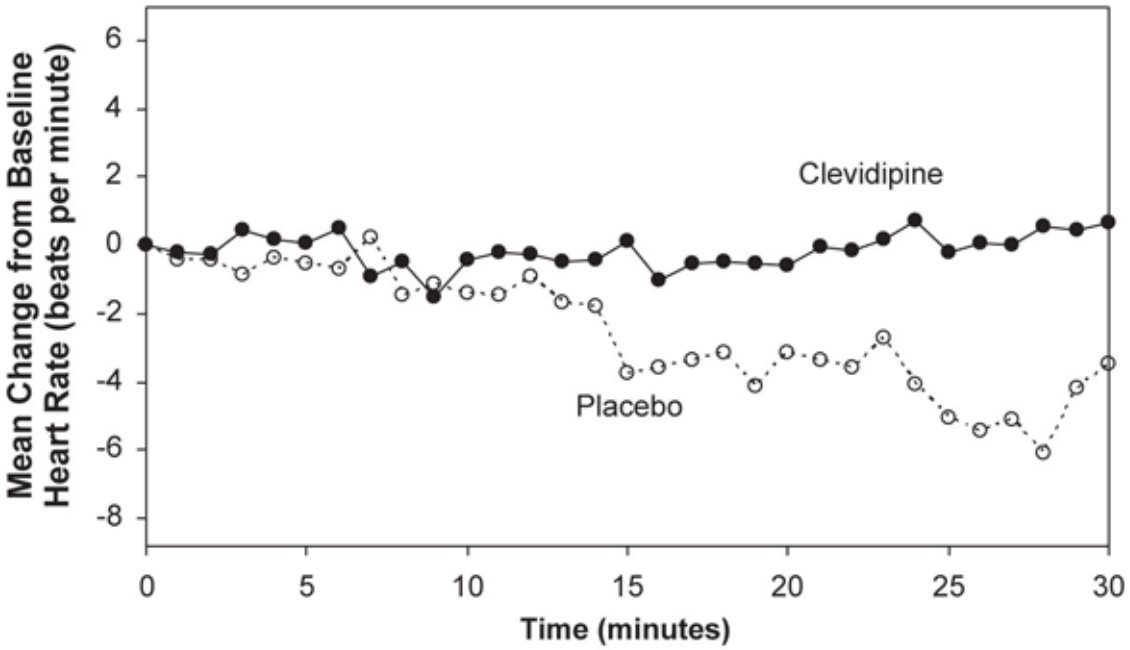


Figure 4. Mean change in heart rate (bpm) during 30-minute infusion, ESCAPE-2 (postoperative)



In three Phase 3, actively controlled, open-label clinical trials (ECLIPSE), 1,506 patients were randomised and received Cleviprex (n=752), nitroglycerine (NTG; perioperative, n=278), sodium nitroprusside (SNP; perioperative, n=283), or nicardipine (NIC; postoperative, n=193; *not registered in Australia*) for the treatment of hypertension in cardiac surgery. The mean exposure in the ECLIPSE studies was 8 hours at 4.5 mg/hour for the 752 patients who were treated with Cleviprex. Blood pressure control was assessed by measuring the magnitude and

duration of SBP excursions outside the predefined pre- and post-operative SBP target range of 75-145 mmHg and the predefined intra-operative SBP range of 65-135 mmHg. In general, blood pressure control was similar across the four treatment groups. The primary safety endpoint was a comparison of the clinical events of death, myocardial infarction (MI), stroke, and renal dysfunction at 30 days post-surgery. Data regarding the primary safety endpoint are presented in the Adverse Effects section, Table 2.

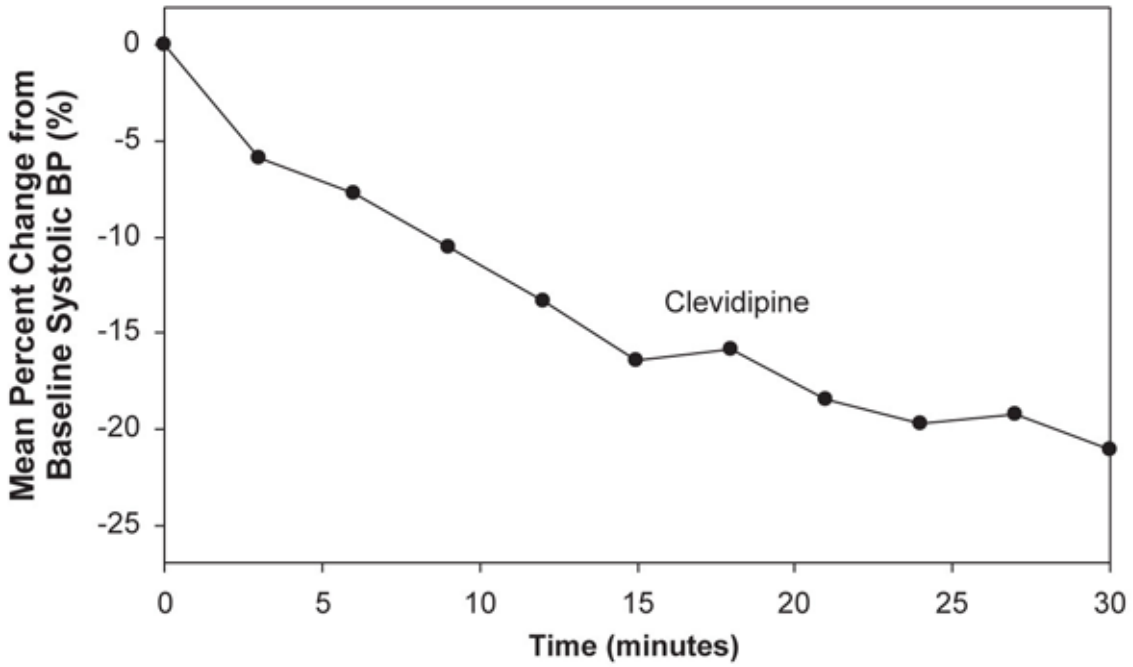
Essential Hypertension
Cleviprex was evaluated in a randomized, placebo-controlled, single-blind, parallel 72-hour continuous infusion study in 61 mild to moderate essential hypertension patients. The mean baseline blood pressure was 151/86 mmHg.

Subjects were randomized to placebo or to 2, 4, 8, or 16 mg/hour. Doses above 2 mg/hour were started at 2 mg/hour and force-titrated in 2-fold increments at 3-minute intervals. Blood pressure, heart rate, and blood levels of clevidipine butyrate were measured during the infusion period. Blood levels were monitored 1 hour after the infusion was discontinued. Blood pressure and heart rate were monitored for 8 hours and also at 96 hours after the termination of infusion. Systolic blood pressure effect was related to the concentration of clevidipine butyrate and plateaued at higher measured concentrations, with the maximal effect estimated at 25% of baseline systolic blood pressure. The estimated infusion rate necessary to achieve half of this maximal effect was approximately 10 mg/hour.

Severe Hypertension
Cleviprex was evaluated in an open-label, uncontrolled clinical trial (VELOCITY) in 126 patients with severe hypertension (SBP >180 mmHg or diastolic blood pressure [DBP] >115 mmHg). Cleviprex infusion was initiated at 2 mg/hour and up-titrated every 3 minutes, doubling up to a maximum dose of 32 mg/hour as required to achieve a prespecified target blood pressure range within 30 minutes (primary endpoint). The transition to oral antihypertensive therapy was assessed for up to 6 hours following cessation of Cleviprex infusion.

The blood pressure effect in this study is shown in Figure 5. The average infusion rate was 9.5 mg/hour. The mean duration of Cleviprex exposure was 21 hours.

Figure 5. Mean percentage change in SBP from baseline during first 30 minutes, VELOCITY



Oral antihypertensive therapy was instituted 1 hour prior to the anticipated cessation of Cleviprex infusion. Transition to oral antihypertensive therapy within 6 hours after discontinuing Cleviprex infusion was successful in 91% (115/126) of patients. No patient had IV antihypertensive therapy reinstituted following transition to oral therapy.

INDICATIONS

Cleviprex is indicated for the short term treatment of hypertension when oral therapy is not feasible or desirable.

CONTRAINDICATIONS

Cleviprex is contraindicated in patients with known allergies to clevidipine, soybeans, soy products, eggs or egg products.

Defective lipid metabolism
Cleviprex should not be used in patients with defective lipid metabolism such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia

Severe aortic stenosis
Cleviprex should not be used in patients with severe aortic stenosis because excessive afterload reduction can reduce myocardial oxygen delivery in these patients.

PRECAUTIONS

Cleviprex should not be used in patients with known allergies to soybeans, soy products, eggs or egg products.

Use strict aseptic technique. Once spiked, begin infusion immediately. Use within 4 hours and discard any unused portion.

Hypotension and reflex tachycardia
Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia that may be associated with a worsening of clinical outcome. If either occurs with Cleviprex, decrease the dose. There is little experience with short-term treatment with beta-blockers for clevidipine-induced tachycardia and beta-blocker use for this purpose is not recommended.

Negative Inotropy
Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure. Monitor heart failure patients carefully.

Beta-blocker withdrawal
Cleviprex does not reduce heart rate and offers no protection against the effects of abrupt beta-blocker withdrawal. Beta-blockers should be withdrawn only after gradual reduction in dose.

Rebound Hypertension
Patients who receive prolonged Cleviprex infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped.

Pheochromocytoma
There is no information to guide use of Cleviprex in treating hypertension associated with pheochromocytoma.

Effects on Fertility
There were no adverse effects on fertility or mating behaviour of male rats at Cleviprex doses of up to 55 mg/kg/day, approximately 5 – 8 times higher than the normal maintenance dose of 4 – 6 mg/h and equivalent to the maximum recommended human dose (MRHD) of 504 mg/day (21 mg/hour x 24-hours) on a body surface area basis. Female rats demonstrated pseudopregnancy and changes in estrus cycle at doses as low as 13 mg/kg/day (similar to the normal maintenance dose and approximately 1/4th the MRHD); however, doses up to 55 mg/kg/day did not affect mating performance or fertility.

Use in Pregnancy - Category C
There are no adequate and well controlled studies of Cleviprex use in pregnant women. Calcium channel blockers can suppress uterine contractions in humans. In animal studies, clevidipine butyrate caused increases in maternal and fetal mortality and length of gestation. Calcium channel blockers as a class carry the potential to produce fetal hypoxia associated with maternal hypotension. Cleviprex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There was decreased fetal survival when pregnant rats and rabbits were treated with clevidipine butyrate during organogenesis at doses 0.7 times (on a body service area basis) the maximum recommended human dose (MRHD) in rats and 2 times the MRHD in rabbits.

In pregnant rats dosed with clevidipine butyrate during late gestation and lactation, there were dose related increases in maternal mortality, length of gestation and prolonged parturition at doses greater than or equal to 1/6 of the MRHD based on body surface area. When offspring of these dams were mated, they had a conception rate lower than that of controls. Clevidipine butyrate has been shown to cross the placenta in rats.

Use in Lactation
It is unknown whether clevidipine butyrate is excreted in human breast milk. The excretion of clevidipine butyrate in milk has not been studied in animals. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Cleviprex should be made taking into account the benefit of breastfeeding to the child and the benefit of Cleviprex therapy to the woman.

Paediatric Use
There is no experience with Cleviprex in children or adolescents. Cleviprex is not recommended in the paediatric age group until further data become available.

Use in the elderly
Of the 1406 subjects (1307 with hypertension) treated with Cleviprex in clinical studies, 620 were ≥ 65 years of age and 232 were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these and younger patients. Although dose adjustment is not required in, elderly patients, doses should be titrated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Carcinogenicity
Long-term studies for evaluation of carcinogenic potential have not been performed with clevidipine butyrate due to the intended short-term duration of human use.

Genotoxicity
Clevidipine butyrate displayed positive genotoxic potential in *in vitro* assays (Ames test, mouse lymphoma thymidine kinase locus assay, chromosomal aberration assay) but not *in*

vivo in the mouse micronucleus test. The positive *in vitro* results are consistent with the formation of formaldehyde, a minor metabolite of clevidipine butyrate, which is known to be genotoxic *in vitro* and a probable human carcinogen. However, human *in vivo* exposure to formaldehyde at the maximum clinical dose of clevidipine (32 mg/h) is at least several hundred times less than normal daily endogenous formaldehyde generation, and is therefore not of clinical concern.

Interactions with other drugs
Pharmacokinetic drug interactions are unlikely as clevidipine butyrate is rapidly metabolised by hydrolysis *in vivo*. No formal drug-drug interaction studies were conducted. Clevidipine butyrate and its major dihydropyridine metabolite appear to have limited potential for inhibiting or inducing any CYP enzyme.

ADVERSE EFFECTS

Cleviprex has been evaluated for safety in 19 completed studies, with 99 healthy subjects and 1307 hypertensive patients who received at least one dose of clevidipine butyrate (1406 total exposures). Clevidipine butyrate was evaluated in 15 studies in hypertensive patients: 1099 patients with perioperative hypertension, 126 with severe hypertension and 82 patients with essential hypertension.

Cleviprex was infused for <24-hours in the majority of patients (n=1199); it was infused as a continuous infusion in an additional 93 patients for durations between 24 and 72 hours.

Perioperative Hypertension
Atrial fibrillation, sinus tachycardia and hypotension were all frequently observed adverse events in the perioperative population. In all Phase III clinical trials on cardiac surgical patients, the incidence of atrial fibrillation in patients treated with Cleviprex as compared to active comparators and placebo was 32.8%, 32.9% and 12.0%, respectively, among which 3.9%, 2.5%, and 0.0% were considered treatment related. The incidence of sinus tachycardia in perioperative patients treated with Cleviprex as compared to active comparators and placebo was 25.5%, 30.5%, and 0.0%, respectively, among which 1.3%, 1.2%, and 0.0% were considered treatment related. The incidence of hypotension in perioperative patients treated with Cleviprex as compared to active comparators and placebo was 15.1%, 14.9%, and 1.0%, respectively, among which 2.5%, 2.5%, and 0.0% were considered treatment related.

The placebo-controlled experience with Cleviprex in the perioperative setting was both small and brief (about 30 minutes). Table 1 shows treatment-emergent adverse events and the category of “any common adverse event” in ESCAPE-1 and ESCAPE-2 where the rate on Cleviprex exceeded the rate on placebo by at least 2% (common adverse events)

Table 1. Common treatment emergent adverse events in placebo-controlled perioperative studies.

	ESCAPE - 1		ESCAPE - 2	
	Clevidipine (N=53) n (%)	**Placebo (N=51) n (%)**	**Clevidipine (N=61) n (%)**	**Placebo (N=49) n (%)**
Patients with at least one TEAE	**38 (71.7)**	**33 (64.7)**	**39 (63.9)**	**28 (57.1)**
Cardiac disorders	**14 (26.4)**	**20 (39.2)**	**20 (32.8)**	**13 (26.5)**
Atrial fibrillation	7 (13.2)	6 (11.8)	13 (21.3)	6 (12.2)
Ventricular tachycardia	2 (3.8)	4 (7.8)	4 (6.6)	2 (4.1)
Tachycardia	2 (3.8)	0 (0.0)	1 (1.6)	4 (8.2)
Ventricular extrasystoles	1 (1.9)	0 (0.0)	3 (4.9)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)
General disorders and administration site conditions	**14 (26.4)**	**8 (15.7)**	**16 (26.2)**	**11 (22.4)**
Pyrexia	10 (18.9)	7 (13.7)	3 (4.9)	3 (6.1)
Oedema peripheral	0 (0.0)	1 (2.0)	4 (6.6)	2 (4.1)
Secretion discharge	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**13 (24.5)**	**9 (17.6)**	**15 (24.6)**	**11 (22.4)**
Atelectasis	3 (5.7)	0 (0.0)	2 (3.3)	5 (10.2)
Pulmonary oedema	2 (3.8)	0 (0.0)	1 (1.6)	4 (8.2)
Wheezing	0 (0.0)	0 (0.0)	4 (6.6)	2 (4.1)
Dyspnoea	0 (0.0)	0 (0.0)	3 (4.9)	0 (0.0)
Psychiatric disorders	**10 (18.9)**	**2 (3.9)**	**15 (24.6)**	**10 (20.4)**
Anxiety	3 (5.7)	1 (2.0)	5 (8.2)	3 (6.1)
Restlessness	2 (3.8)	0 (0.0)	2 (3.3)	0 (0.0)
Disorientation	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	1 (1.9)	1 (2.0)	7 (11.5)	3 (6.1)
Renal and urinary disorders	**7 (13.2)**	**4 (7.8)**	**4 (6.6)**	**4 (8.2)**
Renal failure acute	5 (9.4)	1 (2.0)	0 (0.0)	0 (0.0)
Renal insufficiency	0 (0.0)	2 (3.9)	2 (3.3)	0 (0.0)
Infections and infestations	**7 (13.2)**	**1 (2.0)**	**3 (4.9)**	**1 (2.0)**
Pneumonia	2 (3.8)	0 (0.0)	2 (3.3)	0 (0.0)
Gastrointestinal disorders	**6 (11.3)**	**8 (15.7)**	**17 (27.9)**	**12 (24.5)**
Nausea	3 (5.7)	5 (9.8)	13 (21.3)	6 (12.2)
Constipation	2 (3.8)	1 (2.0)	6 (9.8)	3 (6.1)
Blood and lymphatic system disorders	**6 (11.3)**	**5 (9.8)**	**5 (8.2)**	**3 (6.1)**
Nervous system disorders	**6 (11.3)**	**2 (3.9)**	**2 (3.3)**	**4 (8.2)**
Headache	3 (5.7)	1 (2.0)	1 (1.6)	2 (4.1)
Cerebrovascular accident	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (1.9)	1 (2.0)	2 (3.3)	0 (0.0)
Vascular disorders	**5 (9.4)**	**3 (5.9)**	**3 (4.9)**	**1 (2.0)**
Hypotension	3 (5.7)	1 (2.0)	1 (1.6)	0 (0.0)
Troponin increased	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**1 (1.9)**	**1 (2.0)**	**2 (3.3)**	**0 (0.0)**

Table 2 contains a summary of primary safety endpoint data for the ECLIPSE trials, where clevidipine was compared to nitroglycerine, sodium nitroprusside and nicardipine.

Table 2. Primary endpoint data for the ECLIPSE trials

	Clevidipine (N=752)	**All Active Comparators (N=754)**
Death	20/719 (2.8%)	28/729 (3.8%)
Stroke	8/700 (1.1%)	12/705 (1.7%)
MI	16/700 (2.3%)	17/707 (2.4%)
Renal dysfunction	56/712 (7.9%)	56/710 (7.9%)

The adverse events observed within one hour of the end of the infusion were similar in patients who received Cleviprex and in those who received comparator agents. There was no adverse event that was more than 2% more common on Cleviprex than on the average of all comparators.

Serious Adverse Events and Discontinuation – Perioperative Hypertension Studies
The incidence of adverse events leading to study drug discontinuation in patients with perioperative hypertension receiving Cleviprex was 5.9% versus 3.2% for all active comparators. For patients receiving Cleviprex and all active comparators the incidence of serious adverse events within one hour of drug infusion discontinuation was similar.

Adverse drug reactions, defined as adverse events at least possibly causally related to Cleviprex (Table 3: Perioperative hypertension; Table 4: Essential hypertension) reported in excess (>0.5%) in patients receiving placebo and as more than an isolated case in patients receiving Cleviprex in controlled clinical trials, are listed below by system organ class and absolute frequency.

Frequencies are defined as: very common >1/10; common >1/100, <1/10; uncommon >1/1000, <1/100. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3. Adverse drug reactions in perioperative hypertension patients

Psychiatric disorders	
Uncommon:	Anxiety, Confusional state, Insomnia
Nervous system disorders	
Uncommon:	Dizziness
Cardiac disorders	
Uncommon:	Atrial flutter, Tachycardia
General disorders and administration site conditions	
Common:	Oedema
Uncommon:	Pain, Chest pain, Peripheral oedema, Pyrexia
Investigations	
Uncommon:	Blood creatinine increased, Aspartate aminotransferase increased

Injury, poisoning and procedural complications	
Uncommon:	Incision site complication

Table 4. Adverse drug reactions in essential hypertension patients

Nervous system disorders	
Very common:	Headache
Common:	Dizziness
Vascular disorders	
Common:	Flushing
Gastrointestinal disorders	
Common:	Nausea
Renal and urinary disorders	
Common:	Polyuria
General disorders and administration site conditions	
Common:	Feeling hot
Investigations	
Common:	Alanine aminotransferase increased

Severe Hypertension
The adverse events for patients with severe hypertension are based on an uncontrolled study in patients with severe hypertension (VELOCITY, n=126).

The common adverse events for Cleviprex in severe hypertension included headache (6.3%), nausea (4.8%), vomiting (3.2%) and pruritus (1.6 %). The incidence of adverse events leading to study drug discontinuation for Cleviprex in severe hypertension was 4.8%.

Less Common Adverse Events in Patients with Severe or Essential Hypertension
Adverse events that were reported in <1% of patients with severe or essential hypertension included:
Cardiac: myocardial infarction, cardiac arrest
Nervous system: syncope
Respiratory: dyspnea

A summary of available post-marketing unexpected serious adverse drug reactions is provided in Table 5. Reported rates are based on estimated exposure data and are defined as: rare >1/10000, <1/1000; very rare <1/10000. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5. Unexpected serious adverse drug reactions reported post-marketing

Immune System disorders	
Rare:	Hypersensitivity
Nervous system disorders	
Very rare:	Cerebrovascular accident
Cardiac disorders	
Rare:	Arrhythmia
Very rare:	Atrial fibrillation, Cardiac failure congestive
Gastrointestinal disorders	
Rare:	Ileus
Respiratory, thoracic and mediastinal disorders	
Rare:	Respiratory gas exchange disorder
Skin and subcutaneous tissue disorders	
Very rare:	Rash, Urticaria
General disorders and administration site conditions	
Rare:	Death
Very rare:	Chills
Investigations	
Rare:	Oxygen saturation decreased
Very rare:	Heart rate decreased, Pulse absent, Venous oxygen saturation decreased

Failure to practice appropriate aseptic technique may lead to contamination of infused product and the potential for systemic infection.

DOSAGE AND ADMINISTRATION

Cleviprex should not be used in patients with known allergies to soybeans, soy products, eggs or egg products.

Monitoring

Cleviprex should be administered in a hospital setting with appropriate personnel and capabilities for monitoring blood pressure and heart rate. Monitor blood pressure and heart rate continually during infusion, and then until vital signs are stable. Patients who receive prolonged Cleviprex infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped. These patients may need follow-up adjustments in blood pressure control.

Adults/Elderly

Cleviprex is intended for intravenous use in a hospital setting only. Titrate drug to achieve the desired blood pressure reduction. Individualise dosage depending on the blood pressure to be obtained and the response of the patient.

The duration of treatment may vary according to individual needs of the patient. In patients undergoing cardiac surgery in the ESCAPE trial (versus placebo) the mean (± SD) duration of therapy was 0.50 (± 0.22) hours. In patients undergoing cardiac surgery in the ECLIPSE trial (versus active comparators) the mean (± SD) duration of therapy was 8.23 (± 11.24) hours, whilst for severely hypertensive patients in the VELOCITY trial the mean (± SD) duration of therapy was 21.26 (± 6.64) hours. There is little experience with infusion durations beyond 72 hours.

Initial dose: Initiate the intravenous infusion of Cleviprex at 1-2 mg/h; the dose may be doubled every 90 seconds initially. As the blood pressure approaches goal, the increase in doses should be less than doubling and the time between dose adjustments should be lengthened to every 5-10 minutes. Continue titration until desired target range is achieved.

Maintenance dose: The desired therapeutic response for most patients occurs at doses of 4-6 mg/h. Patients with severe hypertension may require doses up to 32mg/h but there is limited experience at this dose rate.

Maximum dose: The maximum recommended dose is 32 mg/h although most patients were treated with maximum doses of 16 mg/h or less. Because of lipid load restrictions, no more than 1000 mL or an average of 21 mg/hour of Cleviprex infusion is recommended per 24-hour period. In clinical trials, 55 hypertensive patients were treated with > 500 mL of Cleviprex infusion per 24-hour period. There is little experience with infusion durations beyond 72 hours at any dose.

Transition to an oral antihypertensive agent: Discontinue Cleviprex or titrate downward while appropriate oral therapy is established. When an oral antihypertensive agent is being instituted, consider the lag time of onset of the oral agent's effect. Continue blood pressure monitoring until desired effect is achieved.

Special populations

Special populations were not specifically studied. In clinical trials, 78 patients with abnormal hepatic function (one or more of the following: elevated serum bilirubin, AST/SGOT, and/or ALT/SGPT) and 121 patients with moderate to severe renal impairment were treated with Cleviprex. No dose adjustment is required in patients with hepatic or renal impairment.

Paediatric population

There is no experience with Cleviprex in children or adolescents. Cleviprex is not recommended in the paediatric age group until further data become available.

Patients on other lipid-based therapies
Cleviprex contains approximately 0.2 g of lipid per mL (2.0 kcal). In patients with lipid load restrictions the quantity of concurrently administered lipids may need to be adjusted to compensate for the amount of lipid infused as part of the Cleviprex formulation.

Instructions for Administration
Cleviprex is for single use in one patient only. Strict aseptic technique must be maintained while handling Cleviprex. Cleviprex is a single-use parenteral product that contains phospholipids and can support the growth of micro organisms. Do not use if contamination is suspected. Once spiked, begin infusion immediately. Use within 4 hours and discard any unused portion.

Cleviprex is a sterile, white opaque emulsion. Visually inspect for particulate matter and discolouration prior to use. Solutions that are discoloured or contain particulate matter should not be used.

Gently invert vial before use to ensure uniformity of the emulsion prior to administration.

Cleviprex may be administered using a syringe or volumetric pump. Commercially available standard plastic cannulae may be used to administer the infusion. Cleviprex can be administered via a central line or a peripheral line.

Protection from light during administration is not required.

Cleviprex should not be diluted.

Cleviprex should not be administered in the same line or injection site as other medications. However, when using separate injection sites, Cleviprex can be administered with the following:

- Water for Injection, USP
- Sodium Chloride (0.9%) Injection, USP
- Dextrose (5%) Injection, USP
- Dextrose (5%) in Sodium Chloride (0.9%) Injection, USP
- Dextrose (5%) in Ringers Lactate Injection, USP
- Lactated Ringers Injection, USP
- 10% amino acid

OVERDOSAGE

The expected major effects of overdose would be hypotension and reflex tachycardia. Discontinuation of Cleviprex leads to a reduction in antihypertensive effects within 5 to 15 minutes. In case of suspected overdosage, Cleviprex should be discontinued immediately and the patient's blood pressure should be supported.

Contact the Poisons Information Centre on 13 11 26 (Australia only), or the National Poisons Centre on 0800 764 766 (New Zealand only), for advice on management of overdose.

PRESENTATION

Cleviprex is supplied in sterile, single-use, pre-mixed 50 mL and 100 mL glass vials.

Cleviprex is supplied in single vials inside a carton. Each pack includes 10 cartons containing single-use vials.

STORAGE CONDITIONS

Store at 2-8°C. Do not freeze. Protect from light. Vials in cartons may be transferred to controlled room temperature (store below 25°C) for a period not to exceed 2 months. Upon transfer to room temperature, the vials in cartons must be marked with the date the product was removed from the refrigerator. The product must be used or discarded within 2 months of this date or the labelled expiry date (whichever date comes first). Do not return to refrigerated storage after beginning room temperature storage.

NAME AND ADDRESS OF THE SPONSOR.

Kendle R & D Pty Limited
156-158 Drummond Street
Oakleigh
Victoria Australia 3166

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF TGA APPROVAL

09 APRIL 2010

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au