Public Assessment Report

Decentralised Procedure

Cleviprex 0.5 mg/ml emulsion for injection

Clevidipine

PL 16881/0003

UK/H/2477/001/DC

The Medicines Company UK Ltd
LAY SUMMARY
Cleviprex 0.5 mg/ml emulsion for injection
(clevidipine)

This is a summary of the public assessment report (PAR) for Cleviprex 0.5 mg/ml emulsion for injection (PL 16881/0003; UK/H/2477/001/DC). (Cleviprex 0.5 mg/ml emulsion for injection will be referred to as Cleviprex 0.5 mg/ml injection in this report). It explains how Cleviprex 0.5 mg/ml injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Cleviprex 0.5 mg/ml injection.

For practical information about using Cleviprex 0.5 mg/ml injection, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Cleviprex 0.5 mg/ml injection and what is it used for?
Cleviprex 0.5 mg/ml injection is used to lower blood pressure in adults preparing for surgery, undergoing surgery or immediately after surgery.

How does Cleviprex 0.5 mg/ml injection work?
Cleviprex 0.5 mg/ml injection contains the active substance clevidipine, which belongs to a group of medicines called ‘calcium channel blockers’. This active substance works by blocking proteins in the smooth muscle of arteries that cause contraction of these muscles. By reducing the contraction of the smooth muscle, the resistance of the arteries against the blood flow is reduced and the pressure of the blood is reduced.

How is Cleviprex 0.5 mg/ml injection used?
The pharmaceutical form of Cleviprex 0.5 mg/ml injection is an emulsion for injection. Cleviprex 0.5 mg/ml injection will be administered to the patient by a doctor. It will be administered as a continuous infusion (drip) into the vein, where the drug is given to the patient over a long period of time.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The dose and duration of the infusion will depend upon the kind of treatment that the patient is undergoing.

Cleviprex 0.5 mg/ml injection can only be obtained with a prescription.

What benefits of Cleviprex 0.5 mg/ml injection have been shown in studies?
The company, The Medicines Company UK Ltd, provided its own data on efficacy and safety studies.

These studies showed that Cleviprex 0.5 mg/ml injection is effective in lowering blood pressure in adults preparing for surgery, undergoing surgery or immediately after surgery.

What are the possible side effects from Cleviprex 0.5 mg/ml injection?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur with using Cleviprex 0.5 mg/ml injection,
please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Why is Cleviprex 0.5 mg/ml injection approved?**
No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Cleviprex 0.5 mg/ml injection outweigh the identified risks, and the grant of a marketing authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Cleviprex 0.5 mg/ml injection?**
A Risk Management Plan (RMP) has been developed to ensure that Cleviprex 0.5 mg/ml injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the PIL for Cleviprex 0.5 mg/ml injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Cleviprex 0.5 mg/ml injection**
Austria, Belgium, Germany, Spain, France, Italy, Luxembourg, the Netherlands, Sweden and the UK agreed to grant a marketing authorisation for Cleviprex 0.5 mg/ml injection on 09 November 2011. The marketing authorisation in the UK was granted on 23 November 2011.

The full PAR for Cleviprex 0.5 mg/ml injection follows this summary.

For more information about treatment with Cleviprex 0.5 mg/ml injection, read the PIL or contact your doctor or pharmacist.

This summary was last updated in January 2015.
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I Introduction
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Cleviprex 0.5 mg/ml injection (PL 16881/0003; UK/H/2477/001/DC) could be approved. This application is submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Belgium, France, Germany, Italy, Luxembourg, The Netherlands, Spain and Sweden as Concerned Member States (CMS).

This is a prescription-only medicine (POM). Cleviprex 0.5 mg/ml injection is indicated for the rapid reduction of blood pressure in the perioperative setting.

This marketing authorisation has been granted in accordance with Article 8(3) of Directive 2001/83/EC, as amended, for a new active substance/new chemical entity; clevidipine has not been authorised within the European Union (EU) thus far.

Problem statement
Acute hypertension, presenting as a medical urgency/emergency or in association with major surgical procedures is a growing and costly clinical condition. Left untreated, sustained acute hypertension is associated with serious clinical sequelae, which are similar in both medical and surgical patients, and involve cerebral, vascular, cardiac and renal risks such as stroke, myocardial infarction, haemorrhage or renal failure and death.

Epidemiology
Perioperative hypertension: Perioperative hypertension is common, especially in cardiovascular surgery (reported incidence 30 to 80%), abdominal aortic surgery (reported incidence 57%), peripheral vascular surgery (reported incidence 29%), and intraperitoneal procedures (reported incidence 8%).
Essential hypertension: Globally, approximately 1 billion patients suffer from essential hypertension.
Severe hypertension
1-2% of patients suffering from essential hypertension will have a hypertensive emergency at some time in their life.

Optimal pharmacologic control of acute blood pressure (BP) requires agents that are rapid in onset, rapid in offset and predictable in their effect. Although numerous intravenous therapies currently exist, none of these agents display all of these ideal characteristics, and frequently multiple agents are required. Treatment choices for acute hypertension rest on several factors in addition to blood pressure (BP) measurement. These include evidence of end-organ damage (e.g., cerebral, cardiac, vascular, renal), presence of comorbidities (e.g., aortic dissection, acute myocardial infarction [MI], bleeding), and ability to ingest and absorb oral agents. Examples of such clinical circumstances include severe hypertension (emergencies and urgencies) in which rapid control of BP is essential to limit or prevent end-organ injury, and perioperative hypertension. Current intravenous (IV) antihypertensive agents do not provide an ideal therapeutic profile.

About the product
Cleviprex 0.5 mg/ml emulsion for injection is a selective dihydropyridine calcium channel antagonist. It is supplied as ready-to-use, sterile, oil-in-water emulsion for intravenous administration. Each mL contains 0.5 mg of clevidipine. The vehicle is identical to that used for Intralipid 20%, which has a long history of use in parenteral nutrition. The drug substance, which is insoluble in water, is dissolved in the oil phase of the emulsion.
Clevidipine is a rapidly-acting vascular- and arterial-selective 1,4-dihydropyridine L type calcium channel antagonist with an ultra-short half-life. Mean arterial blood pressure (MAP) is reduced by decreasing the systemic vascular resistance via relaxation of arteriolar smooth muscle. This effect is mediated by the selective inhibition of calcium influx through L-type calcium channels. Clevidipine does not cause negative inotropic or chronotropic effects. There is no reduction in cardiac filling pressure (preload), confirming lack of effects on the venous capacitance vessels. Clevidipine is formulated as a lipid emulsion in 20% soybean oil (composition similar to Intralipid®, a fat emulsion that is administered for parenteral nutrition).

**General comments on compliance with GMP, GLP, GCP, agreed ethical principles, pharmacovigilance and environmental risk assessment**

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The GLP status of the safety pharmacology studies is not stated in the reports. Some of the safety pharmacology data were obtained from non-GLP primary pharmacodynamic studies.

All pivotal toxicology studies were stated to be in compliance with GLP regulations and/or with OECD principles of GLP. There were a number of minor exceptions to GLP compliance, such as analyses of test articles that were stated to be in compliance with GMP. Overall, these are unlikely to affect the conclusions of the studies. A number of studies were conducted in Canada, which does not have a GLP monitoring authority for pharmaceuticals and, therefore, there is no obligation to accept the data from these studies.

The RMS has been assured that all clinical studies were conducted in accordance with ICH-GCP guidelines.

A summary of the pharmacovigilance system and a Risk Management Plan (RMP) has been provided with this application and are satisfactory.

An Environmental Risk Assessment (ERA) has been conducted and is satisfactory.

**Paediatric Investigation Plan**

In accordance with Regulation 1901/2006, as amended, the applicant has submitted a Paediatric Investigation Plan (PIP) with this MA application. The European Medicines Agency approved the PIP and granted a deferral on 23 February 2009. The deferral stipulates that the results of paediatric studies may be provided after the MA is approved in adults and that the studies detailed in the PIP should be completed by February 2016. This is acceptable.
Periodic Safety Update Report (PSUR)
A PSUR submission cycle of 6 months has been agreed for this product; this is appropriate.

Approval dates
The RMS and CMSs considered that this application could be approved at the end of procedure (Day 209) on 09 November 2011. After a subsequent national phase, a licence was granted in the UK on 23 November 2011 to The Medicines Company UK Ltd.
II Quality aspects

II.1 Introduction
The application is submitted according to Article 8(3) of Directive 2001/83/EC, as amended, for a new active substance/new chemical entity; clevidipine has not been authorised within the EU thus far.

Cleviprex 0.5 mg/ml for injection is a white, opaque, oil-in-water emulsion for injection with a pH of 6.0–8.8 and an osmolarity of 366 mOsmols/kg. One 50 ml vial of emulsion contains 25 mg clevidipine and one 100 ml vial of emulsion contains 50 mg clevidipine.

The drug product also contains the pharmaceutical excipients soya-bean oil (refined), glycerol, egg phospholipids, water for injections and sodium hydroxide (for pH adjustment).

All excipients comply with their respective Ph Eur monograph, with the exception of the purified egg yolk phospholipids, for which an adequate specification is applied.

Cleviprex 0.5 mg/ml emulsion for injection is packaged in single-use, pre-mixed 50 ml or 100 ml Type I glass vials, sealed with a black elastomeric stopper and capped with a flip-off aluminium overseal. Vials are further packed into cartons in quantities of 10.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

II.2 Drug Substance
General information
INN: clevidipine
Chemical Name: Butanoyloxymethyl methyl rac-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate;

Structure:

![Structure of Clevidipine](image)

Molecular formula: C\textsubscript{21}H\textsubscript{23}Cl\textsubscript{2}NO\textsubscript{6}
Molecular weight: 456.3 g/mol
Appearance: white to off-white solid.
Solubility: insoluble in water, sparingly soluble in 99.5% ethanol and slightly soluble in soybean oil.

Clevidipine is a racemic mixture of (+)-S and (-)-R enantiomers. Clevidipine exists as two polymorphic crystalline forms, of which the use of Polymorph A has been justified.
An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance clevidipine.

**Manufacturing process**
Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

**Control of drug substance**
An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis for all working standards have been provided. Batch analysis data are provided and comply with the proposed specification.

**Container closure system**
Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with foodstuffs.

**Stability**
Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**II.3 Medicinal Product**

**Pharmaceutical development**
A satisfactory account of the pharmaceutical development of the product has been provided. The quality expert report has been written by an appropriately qualified author and is a suitable summary of the quality dossier.

**Manufacture of the products**
A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using production-scale batches and has shown satisfactory results.

**Finished Product Specification**
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Stability of the products**
Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for product kept refrigerated at 2-8 °C. For 2 months of this 3 year shelf life the product may be stored below 25 °C, after which the product must be discarded.
II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of Cleviprex 0.5 mg/ml emulsion for injection from a quality point of view.

III Non-clinical aspects

III.1 Introduction
The non-clinical overview has been written by an appropriately qualified author, and is a suitable summary of the non-clinical sections of the dossier.

III.2 Pharmacology
Clevidipine was shown to be a short-acting calcium antagonist, blocking the L-type calcium current in a whole cell voltage clamp study in isolated rabbit myocytes with a Km of 39 nM.

Clevidipine showed selectivity for vascular over myocardial activity when its effects on rat portal vein and papillary muscle were compared in vitro. Clevidipine also inhibited the potassium-induced influx of calcium into cultured cortical neurones from neonatal rats, with an IC50 of 5.8 μM. Other calcium channel blockers have been reported to show similar neuroprotective effects.

In spontaneously hypertensive rats (SHR), clevidipine and its enantiomers H190/90 and H190/91 showed similar antihypertensive potency and recovery time. Consequently, the racemate has been developed for use.

Clevidipine was five times more potent in SHR than in normotensive rats.

It was more potent (about 10 times) in anaesthetised rats compared with conscious SHR, possibly due to the baroreflex in the conscious animals counteracting clevidipine-induced reduction in blood pressure. No arrhythmias or other ECG changes were seen in conscious SHR, and there were no changes in acid-base balance, plasma electrolytes, blood gases or body temperature.

In conscious normotensive dogs, the dose of clevidipine required to reduce MAP by 20% was 20-30 nmol/kg/min. As in the rat, heart rate increased and was considered to be a result of baroreflex activation.

The study in anaesthetised dogs showed that clevidipine reduces MAP due to a reduction in total peripheral resistance and coronary vascular resistance without changing coronary blood flow and without any negative effects on cardiac contractility or conduction at the tolerated doses.

The safety pharmacology studies have not been conducted in accordance with ICH guidance and are not complete, with respiratory and CNS effects not investigated specifically. The applicant has provided a thorough discussion of the data on safety pharmacology endpoints that have been obtained from non-clinical pharmacology and toxicology studies as well as clinically. The effects of clevidipine on cardiovascular, respiratory, CNS and renal function have all been addressed. In addition, clevidipine is unlikely to interact with the hERG channel to cause QT prolongation. Deviation from the guidance has been discussed.
adequately, and the absence of some studies has been fully justified. No additional \textit{in vitro} or \textit{in vivo} safety pharmacology studies are warranted.

Cardiovascular studies, investigating the primary pharmacodynamic effects did not reveal ECG disturbances in conscious SHR or in anaesthetized dogs, and blood gases and pH and plasma electrolyte levels in SHR.

In anaesthetised rats, infusion of clevidipine at a dose that did not affect blood pressure (2 nmol/kg/min, and, therefore, less than the proposed therapeutic dose of 10-15 nmol/kg/min) had no effect on renal function, apart from a natriuresis. This has also been reported for other calcium antagonists. At higher doses, urinary flow, renal blood flow and GFR were decreased. The effects had generally reversed by the end of a vehicle infusion period following the clevidipine infusion.

In another study in anaesthetised normotensive rats, clevidipine was shown to cause renal vasodilation. At high doses, which reduce blood pressure below the lower limit for renal blood flow autoregulation, renal blood flow falls. The effects are reversible once the infusion ceases.

At therapeutic doses in conscious normotensive rats, clevidipine did not affect gastric emptying or intestinal propulsion, although both functions were inhibited at higher doses.

Clevidipine had no effect on neuromuscular control or the contractile function of skeletal muscle \textit{in vitro}. Clevidipine inhibited the contractile response of the rat portal vein to the stimulants noradrenaline, acetylcholine, serotonin, prostaglandin F2α and angiotensin I with a similar potency to its inhibition of spontaneous contractions in this preparation, suggesting that it had no effect on the autonomic functions in this tissue.

Clevidipine had no effect on body temperature and did not increase bleeding time in conscious and anaesthetised rats and SHR, respectively, at doses that reduced blood pressure significantly.

### III.3 Pharmacokinetics

The limit of quantification (LOQ) given in a publication of the assay method for clevidipine in blood was 0.5 nmol/L and for M1 was 50 nmol/L. The pharmacokinetic written summary states that the LOQ for both clevidipine and M1 is 50 nmol/L (23 ng/ml for clevidipine and 18 ng/ml for M1), and study 1312-226 (4-week toxicity study in the rat) gives the LOQ as 5.0 nmol/L for clevidipine. These different values for the LOQ for clevidipine are a result of improvements in the analytical techniques throughout the development programme.

The blood concentration of clevidipine at steady state increases in proportion to dose over the range studied in rats and dogs, and there are no effects of gender in these species. Elimination is biphasic following termination of drug infusion, with a very short initial half-life of <1 minute in rats, dogs and rabbits (representing at least 80% of the total clevidipine AUC following a single dose), and a longer but still rapid terminal half-life (3 minutes in rabbits, 13 mins in dogs). Clearance is rapid (0.3 L/min/kg in rats and rabbits and 0.5 L/min/kg in dogs).

Metabolite M1 accumulated during a twelve hour infusion of clevidipine in rats, reaching concentrations that were 1800 to 3500 times those of clevidipine at steady state. In dogs, there was no accumulation of M1, either during a 12 hour infusion or throughout the 28-day
In anaesthetised dogs, M1 had not reached steady state before the end of an infusion (three increasing doses for 45 minutes each) in approximately half of the animals. Administration of M1 to rats revealed biexponential decline in blood levels, low clearance compared with the parent molecule and a sex difference; females having a lower clearance and longer terminal half-life. This is contrary to the 28-day toxicity study when rats were administered clevidipine and concentrations of M1 showed no gender differences, although this may have been due to a paucity of data points; some incomplete data sets were excluded from analysis and statistical significance was not demonstrated, although individual females had higher levels of M1 than males. A difference in glucuronidation was suggested as a possible explanation for the sex difference in the pharmacokinetics of M1, as glucuronidation has been reported to be higher in male than in female rats.

Clevidipine is highly plasma protein-bound (>99.5% in human, rat, dog, rabbit and pig) and was independent of concentration over the range studied (25 to 250 nM).

Clevidipine-associated radioactivity was widely and rapidly distributed following an intravenous dose of radiolabelled material. Following intravenous infusion of $[^3H]$-labelled clevidipine in male rats, highest levels of radioactivity were seen in the blood immediately after infusion, with rapid distribution to other tissues including connective tissues, where it remained for 1 to 2 days. There were high levels in the pigmented layer of the eye for up to 2 days, but no binding to melanin pigment in hair roots. Radioactivity crossed the blood-brain barrier. All radioactivity was eliminated by 8 days post-infusion in this study, via the urine and bile. In pregnant (pigmented) rats, there was limited transfer of radioactivity into the fetus following a single intravenous dose.

A more recent study used $[^14C]$-clevidipine, with the radiolabel on the side chain that forms formaldehyde on hydrolysis of clevidipine, so that the fate of the formaldehyde could be followed. Male pigmented and albino rats were used. In the albinos, high levels of radioactivity were associated with the vascular, lymphatic, excretory, metabolic, and secretory tissues, as well as the mucosal lining of the alimentary canal. High levels in urine showed that renal elimination was important. Elimination of radioactivity was not complete in the albino rats, as measurable concentrations of radioactivity remained in most of the sampled tissues/regions at 72 hours, including low concentrations in the testes and accessory sex organs. It was estimated that 2.43% of the dose remained in the tissues and organs of the albino male rat at 72 hours post-dose.

In the pigmented rats, the distribution pattern of $^{14}C$ was similar to that in albino rats. However, the uveal tract of the eye (ciliary body/processes, iris, and retina/choroid) reached appreciable concentrations of radioactivity, which declined slowly with time. The $^{14}C$-labelled material measured in the pigmented skin was higher than the levels measured in the non-pigmented skin. Elimination of radioactivity was not complete in the pigmented rats, as measurable concentrations of radioactivity remained in most tissues, including the uveal tract, at 672 hours (28 days) post-dose. An estimated 0.38% of the dose remained in the pigmented male rat at 672 hours post-dose.

The distribution of $^{14}C$ radiolabel in this study, derived from $^{14}C$-formaldehyde following hydrolysis of $[^4C]$-clevidipine, seems most likely to represent incorporation of the label into the single-carbon pool after oxidation of $[^4C]$-formaldehyde to $[^14C]$-formic acid. Formaldehyde is present endogenously and has a half-life of about 1.5 minutes. Compared with the endogenous blood levels and turnover rate of formaldehyde during normal metabolic
processes, the production of formaldehyde from clevidipine is small (about 200 to 300 times lower) and is, therefore, not considered likely to have an adverse effect on endogenous processes.

In the studies in pigmented rats, radioactivity ($^3$H and $^{14}$C) was associated with the melanin-containing tissues in the eye and skin. Although it is distributed to the skin and eyes, the potential for phototoxicity would appear to be very low or negligible. Clevidipine was shown to be photochemically stable, and light scattering and absorption by pigments in the skin and eye will limit the irradiation of clevidipine. The absence of specific phototoxicity studies is justified.

Low levels of radioactivity were associated with CNS tissues in both albino and pigmented rats. Safety pharmacology studies were not conducted to investigate possible effects of clevidipine on the CNS. The applicant states that during continuous intravenous infusion, behavioural or histopathological changes might occur as a consequence of the continuous infusion instrumentation, which would make minor drug-induced effects difficult to detect. No gross behavioural changes were seen in the toxicity studies in rats and dogs that were related to clevidipine at doses approximately seven times the anticipated therapeutic dose in patients. This argument can be accepted, given the low levels in the CNS and the results of the toxicology studies that showed the lipid vehicle and the infusion process to cause a number of the effects seen and confound the possible effects of clevidipine at doses higher than those needed to produce a pharmacological effect.

No studies were conducted into the distribution into milk.

Clevidipine hydrolyses quantitatively in rat, dog and human blood in vitro to the main metabolite M1 (H 152/81). The half-life of the hydrolysis differs between species but not between sexes. The hydrolysis to M1 also forms formaldehyde, which is discussed above.

Atypical pseudocholinesterase subjects take about twice as long to hydrolyse clevidipine in vitro; the applicant suggests that as the hydrolysis is rapid anyway, the slower reaction is unlikely to be a problem in these individuals. This appears to be an acceptable argument, particularly as it is also noted that clevidipine will be titrated to achieve the desired correction in blood pressure in the individual patient, which should minimize any effects resulting from differences in clearance.

In vivo, clevidipine is extensively metabolised in the rat and dog, with little parent compound detectable in excreta.

There are four main metabolic pathways, namely; ester hydrolysis to M1, and subsequent oxidation of the dihydropyridine ring to the corresponding pyridine (M2), acyl-glucuronidation (to diastereomers M3a and M3b), decarboxylation (to M4) and, in addition, M4 is spontaneously oxidized to the pyridine M5. The main metabolite in rat urine was M2, and in dog urine was M3a and M3b. M5 was the main metabolite in the faeces of both species. In bile duct-cannulated rats and dogs, the main peaks in the bile samples from both species were metabolites M3a and M3b.

Clevidipine was also extensively metabolised in human (male) volunteers, with the same pattern of metabolites as in rats and dogs (mainly M1 in plasma, and M3a, M3b and M5 in excreta). Therefore, rats and dogs are appropriate species in which to study the toxicology of clevidipine.
However, metabolite M6, a glucuronide of a hydroxy diacid, was also identified in humans but was not apparent in the animal species. As a glucuronide metabolite it is unlikely to have any additional toxic effects. The formation of M6, in fact, appears to increase clearance of clevidipine in humans and, therefore, may improve safety rather than increase toxicity.

There appears to be little scope for induction or inhibition of cytochrome P450 isoforms by clevidipine or M1 at therapeutically relevant concentrations.

The radioactivity associated with an intravenous dose of \(^{3}\)H-clevidipine is mainly excreted via faeces in rats and dogs, suggesting biliary elimination is a major pathway in these species, although a significant amount is eliminated via the urine too. This is in line with the distribution studies in rats, showing high levels of radioactivity in urine. In man, the pattern is different in that the urine is the major route of elimination, and the majority of the dose is eliminated more quickly (within 24 rather than 72 hours).

In Study 2131-0121 (metabolism and excretion in dogs following a single intravenous dose of \(^{3}\)H-clevidipine), about 12% of the radioactivity in the faeces corresponded to the retention time of clevidipine in the reversed phase liquid chromatography system. As clevidipine is understood to be broken down almost immediately in the blood to form H 152/81 and formaldehyde, the radioactivity is more likely to represent M5, which has similar hydrophobicity to clevidipine and is the main metabolite of clevidipine in dog faeces.

Clevidipine would appear to have a low propensity for pharmacokinetic interactions with other drugs due to its metabolism by pathways that do not involve cytochrome P450 isozymes. Neither clevidipine nor M1 showed clinically relevant induction or inhibition of cytochrome P450 isozymes. There is a potential for interaction with the neuroblockers vecuronium bromide and pancuronium bromide, although this was described as a small possibility of minor clinical relevance.

### III.4 Toxicology

#### Single dose toxicity

In single dose toxicity studies in rats and mice, decreased motor activity, irregular breathing and injection site irritation were seen. In some cases the injection site irritation was associated with necrosis and was severe enough to warrant sacrifice of the animal. The vehicle used in these studies was dimethylacetamide (DMA)/water 80/20, which may have contributed to the findings. Intralipid is proposed for clinical use. However, the lowest value for the maximum non-lethal dose obtained in these studies (< 92mg/kg, the lowest tested dose in female rats), is about 10-fold the maximum daily human dose of 9.6mg/kg and, thus, provides a reasonable safety margin.

#### Repeated dose toxicity

Repeated dose studies were conducted in rats and dogs, which are appropriate species as shown in the metabolism studies. All studies administered clevidipine by intravenous infusion. Intralipid was used as the vehicle in most of these studies and gave rise to a number of effects, including clinical signs (laboured respiration, decreased activity), changes in haematological and chemistry parameters and histopathological findings in lung, liver, spleen and adrenal gland. Some of these findings may have been increased in the presence of clevidipine in some studies, but largely appear to result from overload of lipid or the presence of the catheter for intravenous infusion of the dose.
Decreased food consumption was seen in the rat studies in all groups receiving vehicle (Intralipid) and, as body weight was not affected, this could probably be explained by the additional nutritional value of the Intralipid.

In a 1-month rat study, clevidipine may have exacerbated some of the effects of Intralipid in the liver and adrenal gland, and it increased heart weight. Corneal opacities were seen in vehicle- and clevidipine-treated groups. There were injection site changes in all groups, including the controls. This study appeared to be confounded by inflammatory reactions and infections and deaths in all but the saline control group and the results were not easily interpreted. A 7-day study was subsequently conducted in rats to investigate the corneal opacities, but these were not found in this study, nor in subsequent 14-day and 1-month studies in rats. Neither were any ocular findings seen in the dog studies, so the ocular findings of the previous study may have been related to the implanted cannulae rather than clevidipine.

Antibiotics were administered to rats in the 14-day study between insertion of the catheter and the start of dosing in an attempt to avoid the problems encountered in the 1-month study. Intralipid vehicle appeared to be responsible for the reduction in food consumption, mild haematological changes and a decrease in urine volume, whereas clevidipine appeared to cause minor increases in total serum bilirubin, serum glucose and serum cholesterol concentrations, as well as an increase in mean heart and liver weights. Ischaemic liver changes and lipid accumulation in alveolar macrophages were seen in the mid- and high-dose clevidipine groups, but the applicant attributed this to the procedure rather than to the administration of clevidipine. The liver changes may have been a result of the continuous intravenous infusion, the location of the catheter in the vena cava leading to reductions in the liver blood flow that, in turn, may lead to local inflammatory reaction and adhesion of the liver lobes.

In a second 1-month rat study, with a 1-month recovery period, continuous IV infusion was used at doses of 23, 39 and 66 mg/kg/day. Intralipid caused decreased food consumption and changes in some haematology and chemistry parameters. Effects attributable to clevidipine were an increase in water consumption (dose-related) and urine volume and, at the mid- and high-dose, an increase in adrenal weight in males and ovary weight in females. Changes in urine volume were also seen in the safety pharmacology studies and are a result of the pharmacological activity of clevidipine. The NOAEL for clevidipine was the low dose of 23 mg/kg/day (50 μmol/kg/day) in this study.

In the dog dose range-finding (5-day) study, Intralipid vehicle had effects on cholesterol levels and the liver, which were also seen in some clevidipine groups, and clevidipine-induced peripheral vasodilatation, increased heart rate with reduced QT interval and reduced activity. The effects of clevidipine on the cardiovascular system are a result of its pharmacology.

In a 1-month dog study, the vehicle produced a number of effects, such as changes in haematological parameters and clinical chemistry parameters, as well as microscopic findings in the lungs, lymph nodes, urinary bladder and adrenals and at the injection site, which could have been attributable to the volume of vehicle administered; but findings at the injection site and adrenal gland were more frequent in the treated groups and may indicate an effect of clevidipine. Clevidipine increased heart rate and decreased QT interval, reduced the weight of the testes and increased spleen weight and adrenal weight in females. There were no histological findings associated with the testes or spleen weight changes. In the adrenal
gland, microscopic effects were seen (cortical hyperplasia of the zona glomerulosa), which may be secondary to the hypotensive action of clevidipine and increased function of the renin-angiotensin system to maintain blood pressure.

The positive chronotropic effect in the 5- and 28-day dog studies was more pronounced on the first than on the last day of the study.

In a 14-day study in male dogs to investigate the testicular changes seen in the 1-month study, doses up to 66 mg/kg/day produced findings of hypo/aspermatogenesis, degeneration/atrophy of seminiferous epithelium and mononuclear cell infiltration, but the distribution of the animals with these findings and the fact that they were present in the same animals pretreatment, does not clarify the role of clevidipine in their generation. Changes in the heart at the mid- and high-dose make the low dose of 6.8 mg/kg/day the NOAEL in this study.

Therefore, in the repeated-dose studies in rats and dogs, findings included effects on haematology, blood chemistry, organ weights and histopathological changes in lung, liver, spleen, adrenal gland and injection site, but were not always dose-related or reproducible. A number of these findings could be related to the lipid vehicle and/or the presence of the catheter for continuous intravenous infusion of the dose. Some findings appeared to increase in incidence in the clevidipine groups, but were generally reversible in those studies that included recovery groups. The lipid vehicle to some extent confounded the interpretation of effects due to clevidipine, but, in general, clevidipine effects (changes in fluid balance, heart rate, heart and adrenal histopathology) appeared to be attributable to its pharmacological activity. Any role of clevidipine in the reduced testis weight in dogs in the 1-month study were not clarified in an additional study. However, there were no similar effects in rats, nor effects on male rat fertility.

Toxicokinetics
On the basis of administered dose (mg/kg/day), rats and dogs received clevidipine at levels up to about 7 times that in man. At the NOAEL in these species, the administered dose was about 1 to 2 times that in man.

On the basis of blood concentrations of clevidipine at steady state, exposure in rats was 0.3 times that in humans and exposure in dogs in the 14-day and 28-day studies was 0.9 or 1.9 times, respectively, that in humans receiving the maximum dose of 9.6 mg/kg/day (6.7 μg/kg/min or 32 mg/h for an 80 kg person). The exposure margins are, therefore, low or absent when comparing the maximum human daily dose with the NOAEL in the toxicity studies. Clevidipine is rapidly hydrolysed to the metabolite M1 and exposure margins in relation to this are 0.05 to 0.14 in dogs and 12-fold in rats, in comparison to a human dose of 3.2 μg/kg/min or 16 mg/h for an 80 kg person. Therefore, the exposure margins are considered acceptable; the margin for clevidipine is approximately 1- to 2-fold that in dogs compared with humans and for metabolite M1 is 12-fold in rats compared with humans. A number of effects noted in the toxicity studies appeared to result from administration of high quantities of the lipid vehicle in order to achieve suitably high doses of clevidipine, and the duration of the studies exceeded that intended in clinical practice.

It is also noted that the NOAEL of 23 mg/kg/day (50 μmol/kg/day) in the 1-month rat study is 1000 times the dose of 50 nmol/kg that reduces arterial blood pressure in rats.
Genotoxicity

Ten *in vitro* studies and one *in vivo* study were conducted to investigate the genotoxic potential of clevidipine.

Clevidipine is hydrolysed rapidly to form the metabolite M1 (H 152/81), releasing equimolar quantities of formaldehyde, which is genotoxic. A number of the studies were conducted to demonstrate that the formaldehyde was responsible for the genotoxic findings.

The first bacterial mutation test was negative, but did not include all required bacterial strains and was repeated. The repeated test showed positive findings in *Salmonella typhimurium* strains TA98 and TA100 in the presence of metabolic activation. The addition of formaldehyde dehydrogenase (FDH) in a third test did not abolish the positive findings in strain TA100.

A fourth test used the pre-incubation method rather than plate incorporation. There were again positive findings with clevidipine in strains TA98, TA100 and TA102 in the presence of metabolic activation. The addition of formaldehyde dehydrogenase reduced the number of revertants induced by clevidipine and by formaldehyde in this study.

In a study of gene mutations in mammalian cells (thymidine kinase locus in L5178Y mouse lymphoma cell), clevidipine induced dose-related mutations in the presence of metabolic activation. The inclusion of formaldehyde dehydrogenase and nicotinamide adenine dinucleotide abolished this effect.

In a separate study in the same cell system, but using formaldehyde instead of clevidipine, positive results were obtained in both the presence and absence of metabolic activation.

Clevidipine was clastogenic in human peripheral blood lymphocytes in the presence and absence of metabolic activation, but the effect was abolished in the presence of FDH. An increase in mitotic index was seen with clevidipine without metabolic activation, but decreased in the presence of S9 fraction. A lymphocyte transformation test was conducted to determine whether the increase was due to increased DNA synthesis or mitotic arrest. Clevidipine did not increase DNA synthesis in the lymphocyte transformation test.

In the presence of FDH, there were no indications that clevidipine was mutagenic in mammalian cells. However, this was not always the case in the bacterial mutation assays. The variability in effects of FDH in the Ames tests was attributed to a number of factors, including the methodology used (plate incorporation vs. pre-incubation), the quantity of FDH applied and the availability of non-protein sulphhydril groups in the assay medium. This variability was also seen in an investigative study conducted to optimise conditions for the Ames tests with clevidipine. These explanations are acceptable.

Taken together, the results of these *in vitro* studies do suggest that the positive effects seen in bacterial and mammalian cells with clevidipine are likely to be attributable to the formaldehyde formed when the molecule is hydrolysed to metabolite M1.

Two *in vitro* tests were also carried out using batches of clevidipine spiked with impurities. Degradation products are limited in the finished product specification, in line with ICH guideline Q3B(R2), Impurities in new drug products. These degradation products were stated to bear some structural similarities to known genotoxins, and may result in additional or synergistic genotoxic effects to those of formaldehyde.
A bacterial reverse mutation study and a chromosomal aberration test in mammalian cells (human peripheral blood lymphocytes) were carried out using a batch of clevidipine, without and with each degradation product. In the bacterial reverse mutation test, the addition of the degradians did not appear to increase the number of revertants over those induced by clevidipine alone. The inclusion of formaldehyde dehydrogenase reduced the number of revertants. In the mammalian cell assay, clevidipine, with and without degradants, increased aberrant chromosomes to similar extents. In this assay, the addition of formaldehyde dehydrogenase did not abolish the production of aberrant findings, although they appeared to be reduced slightly. The amount of FDH used was stated to be not optimised in this system. The studies concluded that the addition of the degradants did not show any additional or synergistic genotoxic effects to those of formaldehyde formed from clevidipine.

The degradation products were added to the batch of clevidipine at their intended limit in the Finished Product Specification. In the absence of increased toxicity following addition of these substances, they could be considered qualified up to the limit specified in the Finished Product Specification. It is not clear how much of these related substances was present in the batches of drug substances used in the toxicology studies, as specifications appeared to be given as a total limit for all impurities rather than individually. Without knowledge of the levels of individual impurities in the batches, none of these general toxicology studies can be used to further qualify the related substances.

The in vivo micronucleus test in mice following intravenous administration of clevidipine was negative, which provides some reassurance that formaldehyde formed from hydrolysis of clevidipine may be adequately detoxified in vivo.

Crucial to the decision about the possible genotoxicity of clevidipine is whether the amount of formaldehyde released will be great enough to add significantly to the endogenous levels in the body and overload endogenous metabolic processes. This has been discussed by the applicant and is summarised earlier in this report. The arguments presented are reasonable and suggest that there is little likelihood of the formaldehyde released from clevidipine having a detrimental effect on endogenous formaldehyde levels or turnover and, consequently, to contribute to the toxicity of clevidipine when infused at a maximum rate of 32 mg/h.

Reproductive toxicology
In the first male fertility study there were no effects on fertility, but the number of animals was small and the study was repeated using larger numbers of animals. The study conduct appeared appropriate, although it was conducted in Canada, which does not have a GLP monitoring authority for pharmaceuticals. There were several effects on the animals including deaths, which occurred in the vehicle group as well as the treated groups. Clevidipine appeared to increase findings seen in the lungs of some animals in the vehicle group. One of the findings was enlarged testes, although there were no effects on sperm count, motility or morphology, nor on histopathology of the reproductive organs or fertility.

Female fertility study showed effects on oestrous cycle length and pseudopregnancy, but mating performance, fertility and early pregnancy were not significantly different from control (vehicle, Intralipid) animals. However, within all groups, there were individual animals with high pre- or post-implantation losses.
In a dose range-finding study for an embryo-fetal developmental study in rats, the high dose of 66 mg/kg/day caused increased early and late intrauterine deaths and post-implantation loss and decreased placental, litter weight and fetal weights.

In the main rat embryo-fetal developmental study, post-implantation losses occurred only at the mid-dose. Fetotoxicity was evident as a decrease in fetal weight, slight reduction in ossification of paws and increased incidence of slight renal pelvic cavitation in the mid- and high-dose groups (35 and 55 mg/kg/day). Positional limb changes (malrotations) were seen in the low- and mid-dose groups, and tail, limb and digit anomalies were also noted in one litter at mid-dose. Anomalies of the extremities are consistent with the known effects of other calcium blockers. Renal pelvic cavitation has been reported as an effect of antihypertensive agents that inhibit the angiotensin converting enzyme.

In a dose range-finding study in Dutch rabbits, early total litter loss and late abortion at 66 mg/kg/day provided insufficient viable litters for evaluation. The highest dose in the main study was 55 mg/kg/day, but again there were abortions and deaths as well as reduced food and water consumption and reduced faecal production. Excessive mammary tissue was observed in a few animals from all clevidipine-treated groups. This was also seen in the female rat fertility study and has been observed with other calcium antagonists.

There were increased early or late intrauterine deaths and lower fetal body weight at the high dose, but an increased incidence of various skeletal variations (unossified heads of long limb bones, fused, misaligned sternebrae) was seen at the mid-dose too (reduced ossification of the supraoccipital bones and sternebrae). The changes observed were stated to be commonly seen in the rabbit when stressed or at maternally toxic dose levels. However, it is considered that they are a direct effect of clevidipine treatment, and similar findings (embryolethality, fetal toxicity, anomalies of the extremities) have been seen with other calcium antagonists.

An additional study in NZW rabbits again showed effects of Intralipid vehicle. There was a trend to reduced fetal weight and the high dose (55 mg/kg/day) increased abortion rate above historical control levels and increased post-implantation loss. The NOAEL for embryo-fetal development in this study was 35 mg/kg/day.

As for other calcium channel blockers, clevidipine had a clear effect on late pregnancy, producing dystocia and delayed parturition. There were no viable litters at the high dose of 55 mg/kg/day. Surviving pups showed no adverse effects on development or reproductive capacity following clevidipine treatment.

**Local tolerance**

In a local tolerance study, injection site swelling and fibrinous thrombi following intravenous infusion was related to the cannula rather than treatment, as it occurred in a control as well as a treated animal and in the latter animal there had been difficulties with venipuncture in the preceding days of the study. The vehicle (Intralipid) used for subcutaneous administration was mildly irritant. Clevidipine was not irritant to the skin.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**

Given the rapid hydrolysis of clevidipine to the metabolite M1 (that has a log Kow < 4.5 and, therefore, does not require PBT testing), it seems likely that clevidipine will not persist in the environment and further screening is not required.
The maximum consumption of clevidipine per year has been calculated based on analysis of data from hospitals in the UK and Germany, where such procedures are conducted that may require intravenous antihypertensive agents. The figure is 14,500,000 mg/year, which results in an Fpen of 0.000028% (0.00000028).

The maximum recommended dose of Cleviprex is 32mg/h, therefore, the maximum daily dose is 768 mg per day if the infusion is given continuously at this rate for 24 hours. Using the Fpen of 0.00000028, the PEC surface water is calculated to be 0.00011 μg/L and is, therefore, less than the figure of 0.01 μg/L that would trigger a Phase II assessment. A Phase II assessment is not required.

III.6 Discussion on the non-clinical aspects
Adequate justification has been provided for the absence of certain specific safety pharmacology studies, as the end-points have been covered in other toxicity studies. No issues arise regarding the pharmacokinetics of clevidipine. Clevidipine is rapidly hydrolysed to form formaldehyde and the metabolite M1, and the formaldehyde is responsible for the positive effects in some in vitro genotoxicity assays. However, the quantities of formaldehyde generated are lower than endogenous levels and are rapidly detoxified in vivo.

The toxicity of clevidipine has been adequately investigated in appropriate species (rats and dogs). Reproductive toxicity studies have shown effects on embryo-fetal development and parturition that are typical of calcium channel blockers.

Cleviprex is not considered to pose a risk to the environment.

The non-clinical data support the proposed dose and indication and there are no objections to the approval of Cleviprex 0.5 mg/ml emulsion for injection from a preclinical point of view.

IV Clinical aspects

IV.1 Introduction
The clinical development programme consisted of 19 clinical studies both in healthy volunteers and the target patient populations. The target patient populations included in these studies included patients affected by the conditions essential hypertension, perioperative hypertension and severe hypertension.

There were several Phase I studies, seven Phase II studies and six Phase III studies. There were two pivotal efficacy studies and three pivotal safety/efficacy studies. The pivotal efficacy studies were placebo controlled and randomised but open label. Similarly, the active controlled studies were also randomised but open label. The active comparators are those agents in common use for treatment of this condition and are considered appropriate. Overall, the development programme is comprehensive if not all inclusive or exhaustive. CHMP Scientific advice was not sought for the development programme.

IV.2 Pharmacokinetics
The clinical pharmacology of clevidipine has been evaluated in vitro and in vivo (healthy volunteers and patients). The pharmacokinetic (PK) studies were supported by a series of in vitro experiments (biopharmaceutical studies) in whole blood, including clevidipine effect on P450 enzymes, metabolic interaction of clevidipine with other drugs, influence of deficiency
of pseudocholinesterase on elimination rate of clevidipine, and the effect of temperature and
dilution on t\textsubscript{1/2} of clevidipine. In these \textit{in vitro} studies, whilst some induction/inhibition of
CYP450 enzymes has been noted with clevidipine, the concentrations at which these were
achieved were nearly 10-fold higher than those achieved in the human plasma during clinical
trial administration and, thus, their clinical relevance is unclear. Biopharmaceutical studies
also identified a number of agents that are used commonly in cardiac surgical settings as
showing administrative incompatibility; this issue is addressed in the product information,
SmPC and Package insert. This is also addressed in the Risk Management Plan. As
clevidipine is metabolised by non-specific esterases, the effect of pseudocholinesterase
polymorphism was studied using \textit{in vitro} blood specimens in six samples (from three blood
donors) that showed a small effect, unlikely to be of clinical relevance. It was subsequently
clarified that the subjects were identified based on dibucaaine number evaluation and were,
therefore, essentially related to phenotype, albeit with genotypic implication. However, this is
unlikely to be of great clinical relevance due to the marginal impact of the pharmacokinetics
of clevidipine, as the dose is titrated against response.

There were seven PK studies in human subjects, both healthy volunteers (n=104) and patients
(n= 95), involving a total of 217 subjects (some subjects were dosed twice). See below for
details of the methodology of the studies. The studies conducted in healthy volunteers and
their methodologies appear appropriate. As clevidipine is insoluble in water and is
formulated in Intralipid after dissolution in soybean oil, the absence of bioavailability and
bioequivalence studies is not a hurdle to development or Marketing Authorisation grant.
Arterial blood concentrations of clevidipine are approximately twice as high as venous
concentrations. Mean clearance values from venous and arterial samples from patients after
cardiac surgery were 0.09 and 0.05 L/min/kg, and for healthy volunteers were 0.1–0.2 and
0.07 L/min/kg, respectively. After termination of an infusion of clevidipine in healthy
volunteers, the blood concentration declines in a multiphasic pattern. The initial and terminal
t\textsubscript{1/2}, from arterial blood after a final dose rate of 3.2 μg/min/kg (16 mg/h) during short term (20
min) and long term (24 h) infusion (high rate), were 0.6, 15.6 and 0.7, 21.1 minutes,
respectively. The V\text{d} of clevidipine is considerably smaller than other calcium channel
blockers such as felodipine. Hypothermia reduces clearance of clevidipine and this has an
implication for administration during bypass and pre or post-bypass. As the estimated alpha
and beta half-lives are short (1–3 minutes) the small difference in clearance during
hypothermia is unlikely to cause significant issues during administration, especially as MAP
(or SBP) is closely monitored during administration.

Clevidipine is rapidly hydrolysed by non-specific esterases that cleave the ester group,
resulting in equivalent primary metabolite formation (see fig below). Hydrolysis by esterases
occurs in the blood, and potentially also in the vascular endothelium and in extravascular
tissues, to its corresponding pharmacologically inactive carboxylic acid (metabolite M1–
H152/81). The M1 metabolite is further metabolized by glucuronidation or oxidation to the
corresponding pyridine derivative. In man, a mean of 83% of a given radiolabelled dose of
clevidipine is excreted in urine and faeces. The major fraction (63–74%) is excreted in the
urine and 7–22% is excreted in the faeces. More than 90% of the recovered radioactivity is
excreted within the first 72 hours of collection. The studies and results suggest that renal or
hepatic pathway involvement is small to minimal for clevidipine metabolism and excretion.
This will have a bearing on overall administration in those subjects with such concomitant
disease/co-morbidities. Clevidipine is a racemate. The PK properties of the enantiomers H-
190/90 and H-190/91 are essentially the same, as determined from venous blood
concentrations after administration of clevidipine for 4 hours to patients with moderate
essential hypertension.
Dose proportionality, linearity and time dependency of PK parameters were evaluated in several studies, in both healthy volunteers and patients. The patients included both mild to moderate hypertensives and those undergoing cardiac surgery with bypass. These are fairly representative of the target populations for clevidipine use in clinical practise. Although these parameters have not been studied in the severely hypertensive populations, there are no reasons to suspect that pharmacokinetics would be different in this specific population, based on the nature of the agent and its metabolism.

**Fig-1: Blood concentration during steady state vs. dose rate calculated by a linear regression analysis**

The development programme encompasses PK studies in the relevant target populations, including populations affected by mild to moderate hypertension, perioperative hypertension and some severe hypertension. The PK results are consistent with features of a short acting agent that dissipates rapidly due to metabolism, with rapid onset and offset. These are considered appropriate. Of note, demographic features (except for body weight) had little influence on clevidipine distribution, metabolism and overall efficacy.

The applicant has analysed the PK data based on age, gender and ethnicity:

**Gender and clevidipine PK**
In all healthy volunteer studies, 84.8% of subjects were male (M=104, F=18; total of 122). Of these, all PK studies involved only healthy male volunteers. The applicant has provided a gender based analysis of the data for PK parameters. The effect on gender is difficult to quantify using the current dataset due to the large variability of PK parameters. Based on the geometric means of CL, females had an approximately 27% higher clearance than males, but the terminal elimination half-life of clevidipine is approximately the same for both genders.

**Ethnicity and clevidipine PK**
In all healthy volunteer studies, 70.7% of the subjects were Caucasian. While not conclusive, there are some minor differences between different ethnicities, but the numbers are small. A potential effect of race on the CL of clevidipine was observed. Based on the geometric means of the two groups, the values for CL in black or African American subjects were more than twice the value for Caucasians (these results are from one study with limited numbers).

**Age and clevidipine PK**
All individuals in the healthy volunteer studies were <60 years old. In the hypertensive studies, nearly 50% of subjects were >65 years old and ~20% were >75 years (22%; n=26). The overall development programme included ~20% of those with >75 years of age, but very
few in the PK studies. The applicant has not provided direct PK data, although these data were obtained in the Phase III trials (rather than in specific PK-PD studies). Of note, the number of subjects in the older age groups is small, but the applicant has not proposed a change in dosing related to age. This is acceptable in that clevidipine dose is titrated against blood pressure response and, therefore, age related PK changes will have little impact overall. Importantly, the short half-life consistent across age groups provides a level of reassurance.

**Table-1: Descriptive statistics of clevidipine PK comparing subjects aged <65 and >65 years**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CL (L/hr)</th>
<th>V1 (L)</th>
<th>Vss (L)</th>
<th>Terminal Half-life (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td>65 Years Old and Younger</td>
<td>Older Than 65 Years</td>
<td>65 Years Old and Younger</td>
<td>Older Than 65 Years</td>
</tr>
<tr>
<td>N</td>
<td>91</td>
<td>13</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Mean</td>
<td>110.0</td>
<td>1180</td>
<td>18.0</td>
<td>5.36</td>
</tr>
<tr>
<td>SD</td>
<td>831</td>
<td>938</td>
<td>14.6</td>
<td>2.53</td>
</tr>
<tr>
<td>Min</td>
<td>143</td>
<td>153</td>
<td>4.05</td>
<td>1.74</td>
</tr>
<tr>
<td>Max</td>
<td>4500</td>
<td>2900</td>
<td>48</td>
<td>8.36</td>
</tr>
<tr>
<td>CV%</td>
<td>52%</td>
<td>62%</td>
<td>14.6</td>
<td>6.02</td>
</tr>
<tr>
<td>Geometric Mean</td>
<td>785</td>
<td>785</td>
<td>12.6</td>
<td>4.73</td>
</tr>
<tr>
<td>NC</td>
<td>not calculated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Interactions and clevidipine PK**

Clevidipine has shown a very low potential for interaction in the short term administration scheme followed during the development programme. *In vitro* studies have not shown a high potential for PK interaction, either directly or through the CYP450 enzymatic pathways, as clevidipine is metabolised independently. Although clevidipine has shown an ability to inhibit several CYP450 enzymes, these occur at concentrations (Ki) 1000 times that achievable by clinical dosing. Therefore, these are unlikely to be of major clinical significance. Clevidipine is highly protein bound and displacement has not been an issue given its rapid metabolism (inactivation) and offset of effect. A question was raised relating to protein binding and potential for interaction. The applicant has persuasively argued that interaction is very unlikely and any interaction is of very little clinical significance. The arguments are based on the facts listed above. Moreover, in the ESCAPE and ECLIPSE studies, where several concomitant drugs were used with a high potential for displacement/interaction, no difference in adverse event rates or efficacy was noted between those administered clevidipine with or without concomitant agents. These arguments are logical and acceptable.

In summary, therefore, while there appears to be some difference between races in terms of CL, these cannot be generalised as the number of subjects was small, there are little data in other racial/ethnic groups and the range is wide. Many of the parameters were not calculated in these populations. Also, despite the modelling, further analysis of these parameters from efficacy studies did not contribute significantly to enhancing the knowledge regarding these covariates. The applicant incorporated the PD effect ($E_{\text{max}}$ and $E_0$) from the TMC_CLV-06-01 and 06-02 studies to demonstrate that $E_{\text{max}}$ did not differ between the groups tested (analysed) irrespective of the covariate. Based on this, it may be possible to conclude that the minor differences noted between genders and races are of little clinical significance for an agent that is titrated according to blood pressure response.
Special Populations (renal and hepatic impairment)

The hepatic CYP450 enzyme pathways are not involved in clevidipine metabolism and excretion. Similarly, the renal pathway is also minimally involved in the metabolism of clevidipine as such, although the inactive metabolites are excreted via the renal route. An analysis of the clinical dataset has been provided to demonstrate the effect of clevidipine on organ dysfunction and the effect of organ dysfunction on clevidipine PK and efficacy/safety. In clinical trials, 121 patients with moderate to severe renal impairment were treated with Cleviprex.

Table-2: Change from baseline in serum creatinine by renal function (all Phase II and Phase III studies, safety population)

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Treatment</th>
<th>N</th>
<th>Mean (SD)</th>
<th>N</th>
<th>Mean (SD)</th>
<th>N</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 h infusion duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Placebo</td>
<td>79</td>
<td>0.9 (0.21)</td>
<td>78</td>
<td>1.0 (0.26)</td>
<td>78</td>
<td>0.1 (0.21)</td>
</tr>
<tr>
<td></td>
<td>Clevidipine</td>
<td>642</td>
<td>0.9 (0.21)</td>
<td>636</td>
<td>1.0 (0.37)</td>
<td>636</td>
<td>0.1 (0.32)</td>
</tr>
<tr>
<td>Mild</td>
<td>Placebo</td>
<td>46</td>
<td>1.1 (0.23)</td>
<td>45</td>
<td>1.1 (0.28)</td>
<td>45</td>
<td>0.0 (0.22)</td>
</tr>
<tr>
<td></td>
<td>Clevidipine</td>
<td>378</td>
<td>1.1 (0.26)</td>
<td>374</td>
<td>1.2 (0.65)</td>
<td>374</td>
<td>0.1 (0.58)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Placebo</td>
<td>8</td>
<td>1.5 (0.43)</td>
<td>8</td>
<td>2.2 (1.75)</td>
<td>8</td>
<td>2.2 (1.75)</td>
</tr>
<tr>
<td></td>
<td>Clevidipine</td>
<td>84</td>
<td>1.4 (0.43)</td>
<td>84</td>
<td>1.4 (0.50)</td>
<td>84</td>
<td>1.4 (0.50)</td>
</tr>
<tr>
<td>Severe</td>
<td>Placebo</td>
<td>4</td>
<td>6.3 (2.07)</td>
<td>4</td>
<td>5.2 (1.36)</td>
<td>4</td>
<td>1.1 (1.21)</td>
</tr>
<tr>
<td></td>
<td>Clevidipine</td>
<td>25</td>
<td>4.9 (3.51)</td>
<td>24</td>
<td>4.1 (2.51)</td>
<td>24</td>
<td>1.0 (3.31)</td>
</tr>
</tbody>
</table>

The clinical trials included 78 patients with abnormal hepatic function (one or more of the following: elevated serum bilirubin, AST/SGOT, and/or ALT/SGPT). The table below includes 66 of the 78 patients. No dose adjustment is required in patients with hepatic or renal impairment. A description of the data is included in section 4.2 of the SmPC for Cleviprex 0.5 mg/ml emulsion for injection.

Table-3: Change from baseline in ALT levels by hepatic function and duration of clevidipine infusion

<table>
<thead>
<tr>
<th>Hepatic Function</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Day 7 / Last Assessment</th>
<th>Absolute Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
</tr>
<tr>
<td>≥24 h infusion duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Placebo</td>
<td>13</td>
<td>23.1 (14.98)</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Clevidipine</td>
<td>47</td>
<td>21.8 (8.81)</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>All Active</td>
<td>4</td>
<td>19.4 (7.32)</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Placebo</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Clevidipine</td>
<td>2</td>
<td>53.0 (21.79)</td>
<td>2</td>
</tr>
</tbody>
</table>

IV.3 Pharmacodynamics

The development programme addresses the relevant aspects of the pharmacodynamics (PD) of clevidipine. The programme includes different sets of target populations and PD has been explored in healthy volunteers as well to establish the basis. As expected, in those with normal blood pressure (healthy volunteers) the effect on MAP is small but there is appreciable increase in heart rate. The doses of clevidipine administered in these studies ranged from 0.5 to 21.6 μg/kg/min (2.4 to 103.7 mg/h for an 80 kg subject) and the length of infusions ranged from 20 min to 24 h. In those with hypertension, clevidipine was administered in a dose range from 0.1 to 6.7 μg/kg/min (0.5 to 32 mg/h for 80 kg patient) and
the length of infusions ranged from 1 to 96 h. Clevidipine reduces SBP, MAP and DBP in a dose dependent fashion in all target populations studied; essential hypertension, perioperative hypertension and severe hypertension (this will be detailed in the efficacy sections). The main points of interest are; clevidipine is a predominant resistance vessel dilator (arteriolar) and this may offer some advantages. It exhibits a reasonable dose response for reduction of MAP, although the ΔSBP from baseline did not show significant changes with changing doses of clevidipine. The onset of effect is rapid and the time required to establish steady-state concentration and effect is about 2 to 3 minutes. Generally, the time to onset of effect was less than 5 minutes between the start of clevidipine infusion and the attainment of maximal effect on hemodynamic parameters. In all hypertensive patients, the first BP-lowering effects were very rapid (2 to 10 minutes) after starting infusion. The PD effect of clevidipine is better correlated with arterial blood samples than venous samples. Given the limitations of venous samples and the rapid clearance of clevidipine from whole blood, the implication is that blood levels may not have a high clinical utility.

Table-4: PD parameters in the clinical pharmacology studies using various infusions of clevidipine

<table>
<thead>
<tr>
<th>Study (population)</th>
<th>Dose</th>
<th>Length of infusion</th>
<th>PD parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAD-3001* (healthy)</td>
<td>0.24-105.1</td>
<td>20 min</td>
<td>EC50 (mmol/L)</td>
</tr>
<tr>
<td>SAD-3002 (healthy radiolabelled)</td>
<td>26.0-30.9</td>
<td>60 min</td>
<td>N/A</td>
</tr>
<tr>
<td>SAD-3003 (perioperative hypertension)</td>
<td>0.2</td>
<td>122 min</td>
<td>6.25</td>
</tr>
<tr>
<td>SAD-3004 (essential hypertension)</td>
<td>0.48-2.9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SAD-3005* (perioperative hypertension)</td>
<td>a)1.1-105.6, b)1.76-14.4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SAD-3006* (perioperative hypertension)</td>
<td>a)5.3-16, b)4.3-15.8</td>
<td>10 min</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Clevidipine exhibits a clear dose response and concentration-effect relationship. The applicant is right in pointing out that alterations in infusion rates did not always provide a significant change in MAP or SBP at each step as function of change from baseline, but this is not unexpected as the slope of the response curve becomes shallower with increasing doses. The non-weight based dosing strategy proposed is primarily based on a single study but further analysis has been performed and this reporting has not led to safety concerns.

The secondary pharmacology is as expected with a suggestion that clevidipine could offer more in terms of safety and benefit in comparison to SNP as it does not reduce venous return, thereby avoiding reduction in SV and CO. Clevidipine or its metabolite (H152/8I) do not exhibit any effects on cardiac repolarisation. There is no suggestion of reduction in myocardial contractility or a negative inotropic effect, at least from study SAD-0005.
Cardiac repolarisation/ QT Study

The applicant has provided the thorough QT study in line with ICH E-14 requirement for NCEs. The design of the study is complex, as necessitated by the expected increase in HR with clevidipine and the need for adequate correction. The study was conducted in two phases and some aspects (such as QTcB) were un-interpretable due to an increase in HR at therapeutic and supratherapeutic doses of clevidipine. Notably, there is no study on hERG channels in the dossier. However, the lack of effect in the thorough QT study provides sufficient reassurance regarding cardiac repolarisation effect. More importantly, the expected increase in heart rate consequent to decrease in blood pressure (governed by the baroreceptor reflex in most individuals) affords a certain level of protection against QT prolongation and any consequential arrhythmia (at least theoretically).

The main limitation of the SAD-0003 and SAD-0005 studies is their open label design and it is possible that bias could be introduced at several levels, including treatment assignment, analysis etc. The applicant has argued that given the difficulties with a lipid soluble agent and mandatory Intralipid administration, a blinded study design was not feasible.

IV.4 Clinical efficacy

Phase II and III controlled and uncontrolled clinical trials investigated the use of clevidipine as an IV antihypertensive agent in patients that are representative of those that would be expected to receive the medicinal product after marketing. The Phase II studies presented in this efficacy summary include data from more than 400 patients (of which 315 received clevidipine), recruited into nine studies - including three studies in patients with essential hypertension and six studies in patients with perioperative hypertension. The Phase III studies were integrated and included data from more than 1,800 patients (of which 992 received clevidipine) recruited into six pivotal studies, including five studies in patients with perioperative hypertension and one study in patients with severe hypertension.

Table-5: List of Phase III studies – Efficacy (and primary safety studies)

<table>
<thead>
<tr>
<th>Hypertensive patients - Phase III (N=1846)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative hypertension (N=1730)</td>
</tr>
<tr>
<td>TMC-CIV-03-01 ESCAPE-1</td>
</tr>
<tr>
<td>Efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery.</td>
</tr>
<tr>
<td>TMC-CIV-03-02 ESCAPE-2</td>
</tr>
<tr>
<td>Efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery.</td>
</tr>
<tr>
<td>TMC-CIV-03-03 ECPLSE-NIT5</td>
</tr>
<tr>
<td>Chloropride in the perioperative treatment of hypertension assessing safety events (with NIT5 as active comparator).</td>
</tr>
<tr>
<td>TMC-CIV-03-04 ECPLSE-SNP</td>
</tr>
<tr>
<td>Chloropride in the perioperative treatment of hypertension assessing safety events (with SNP as active comparator)</td>
</tr>
<tr>
<td>TMC-CIV-03-05 ECPLSE-NIC</td>
</tr>
<tr>
<td>Chloropride in the postoperative treatment of hypertension assessing safety events (with NICE as active comparator)</td>
</tr>
<tr>
<td>Severe hypertension (N=146)</td>
</tr>
<tr>
<td>TMC-CIV-05-02 VELOCITY</td>
</tr>
<tr>
<td>Evaluation of the effect of clevidipine in the treatment of severe hypertension.</td>
</tr>
</tbody>
</table>

Dose response studies included Phase II studies, which used various infusion rates and included both healthy volunteers and patients with essential or perioperative hypertension. The EC50 estimated in healthy volunteers was 1.4 μg/kg/min (7 mg/h). Healthy volunteers in SAD-0001, tolerated doses of up to 16 μg/kg/min (80 mg/h) without difficulty. A linear relationship between dose and blood concentration was confirmed. A suitable haemodynamic variable (MAP/HR) was derived to reflect changes in systemic vascular resistance. Using an $E_{max}$ model, the relationship between MAP/HR and the dose of clevidipine was explored and the EC50 was calculated to be 1.4 μg/kg/min (7 mg/h). In Phase II, a dose of 0.6 μg/kg/min
(3 mg/h) provided a reduction of 15% in MAP from baseline (SAD-0004). There was a clear dose-effect correlation, with clevidipine doses of 0.32 μg/kg/min (1.5 mg/h) and above (n = 56) being clinically and statistically different from placebo (p<0.05). At the highest dose rate (9.58 μg/kg/min or 46 mg/h), 28% of the patients discontinued therapy due to hypotension. In SAD-0005, the mean dose required to maintain MAP between 70 and 80 mmHg in the postoperative period was 2.27 μg/kg/min (11 mg/h). In SAD-0006, a mean dose of 1.83 μg/kg/min (8.78 mg/h) was required to maintain MAP between 70 and 75 mmHg in the period prior to initiation of cardiopulmonary bypass (CPB).

The applicant has provided further discussion and arguments in favour of the proposed non-weight based dosing as opposed to dosing based on body weight. The data and discussion hinge on the modelling approach using the data obtained from SH-SAD-003, ESCAPE, ECLIPSE trials, supported by data from analysis of the VELOCITY trial in severe hypertensives. The crux of the argument is that non-weight based dosing is consistent with weight based dosing (see table below).

**Table-6: Starting doses in Phase III studies (weight-based and non-weight-based conversion)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight range of subjects (min, max)</th>
<th>Protocol-defined starting dose</th>
<th>Non-weight-based normalised equivalent (80 kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC-CLV-03-01 (ESCAPE-1)</td>
<td>53.8, 150.6</td>
<td>0.4 μg/kg/min</td>
<td>2 mg/h</td>
</tr>
<tr>
<td>TMC-CLV-03-02 (ESCAPE-2)</td>
<td>47.0, 121.0</td>
<td>0.4 μg/kg/min</td>
<td>2 mg/h</td>
</tr>
<tr>
<td>TMC-CLV-03-03 (ECLIPSE-NCT)</td>
<td>43.0, 147.7</td>
<td>0.4 μg/kg/min</td>
<td>2 mg/h</td>
</tr>
<tr>
<td>TMC-CLV-03-04 (ECLIPSE-NBP)</td>
<td>42.0, 159.2</td>
<td>0.4 μg/kg/min</td>
<td>2 mg/h</td>
</tr>
<tr>
<td>TMC-CLV-03-05 (ECLIPSE-NCP)</td>
<td>50.1, 172.3</td>
<td>0.4 μg/kg/min</td>
<td>2 mg/h</td>
</tr>
<tr>
<td>TMC-CLV-06-02</td>
<td>40.9, 204.0</td>
<td>2 mg/h</td>
<td>N/A study dose was non-weight based</td>
</tr>
</tbody>
</table>

**Fig-2: Regression model for dosing up to 32mg/h in support of non-weight based dosing**

The population included in the trials is a fair representation of general groups within that population; essential hypertension, perioperative hypertension and severe hypertension. There were an adequate number of subjects aged 65 and over and ~20% of subjects in the entire database were aged ≥ 75 years. Certain groups who may not be able to mount a compensatory tachycardiac response to drop in SBP or MAP, such as those with primary ventricular pacing or those with left bundle branch block, are excluded. This is considered appropriate as significant arteriolar dilatation (with fall in SBP or MAP) could be detrimental without the compensatory mechanisms. This holds true even with careful titration of clevidipine dose. Of note, certain types of patients (hypertensive emergencies) are not
represented; these include those with pre-eclampsia, aortic dissection, pheochromocytoma and primary renovascular hypertension.

**Control groups**

Placebo control was used in two main Phase III (ESCAPE) efficacy trials in patients with perioperative hypertension, with truncated measurement times, and in several (n=5) Phase II trials. Active comparators were used in all ECLIPSE trials (NTG, SNP and NIC trials). The severe hypertension trial (VELOCITY) was uncontrolled.

**Trial designs**

While the applicant’s arguments for the open label nature of the trials with active comparators could be sympathised with, it should be pointed out that the cardiac surgical setting (operative theatre setting), with its strictly controlled environment, would probably have provided the best opportunity for a successful double dummy trial design for an intravenous agent. Notwithstanding this criticism, the assessor is of the opinion that double dummy design trials are not mandatory, as the applicant used relevant end points rather than BP control alone and this reduces the effect of bias on the overall results. Furthermore, the statistical analyses that have been included do provide sufficient evidence that the applicant has eliminated the sources of bias considerably. Based on these, for the treatment of perioperative hypertension, the open label nature of the studies is not considered a major limitation. For the severe hypertension study (VELOCITY), while the same considerations apply, the absence of a control group does limit the utility and reliability of the study. The patient characteristics could differ and the need to rapidly reduce blood pressure should be seen in the context of overall risk: benefit. The use of AUC of excursion outside of the conventional definitions of normal/controlled blood pressure may reduce the analytical bias, but will not limit bias prior to assignment. It is possible that a number of subjects who would otherwise have fit the inclusion criteria were not included because of the investigators’ reluctance to use a newer agent or a calcium channel blocker. In this context, a randomised assignment would have been preferable with a control arm.

**ESCAPE 1 and 2**

These were Phase III, multicentre, double-blind, placebo-controlled, randomised, parallel-group trials. Patients with a recent history of hypertension, or who were hypertensive upon admission, and who were scheduled for cardiac surgery were eligible for the trial. Patients were randomised, and then treated if they met two post randomisation criteria. The primary endpoint was the incidence of bailout within 30 minutes of start of treatment, and this could be due to three reasons; lack of efficacy, safety reasons or treatment failure. Secondary endpoints were the time until reduction of 15% in blood pressure, change from baseline in mean arterial pressure (MAP) and incidence of bailout by cause. ESCAPE 2 was a trial similar in design to ESCAPE 1 but the setting was in postoperative cardiac surgery patients, rather than the preoperative setting of ESCAPE 1. Bailout was again the primary endpoint, with the other three secondary variables remaining the same. The analysis methods are the same. Again, post-randomisation criteria were employed.

The treatment arms were similar in terms of baseline demographic variables. The median time to treatment success was 6 minutes with clevidipine and with so many patients not achieving blood pressure lowering in the placebo group this median was inestimable. In ESCAPE 2, median time to event was 5.3 minutes in the clevidipine group with, again, the median not being estimable for the placebo group due to the small number of patients who achieved it. There is very strong statistical evidence of efficacy for the lowering and control of blood pressure compared to placebo for clevidipine. The median time until control is 6
minutes, and the effect can be maintained for the entire 30 minutes. 92.5% of patients did not require bailout and were, thus, treatment successes within 30 minutes. The results of ESCAPE 2 again show superiority of clevidipine over placebo, although the results are at first sight slightly less compelling. The main reason for bailout was a lack of efficacy. The secondary endpoint of change in MAP is important and the performance of clevidipine is very similar in ESCAPE 1, although the placebo response is much greater.

**VELOCITY study (severe hypertension)**
The VELOCITY study was an uncontrolled, open-label study examining the efficacy of clevidipine in patients with severe hypertension, defined as SBP >180 mmHg and/or DBP >115 mmHg assessed on two successive occasions, 15 minutes apart. This was primarily designed as a safety trial, although efficacy endpoints were measured. Patients were enrolled until approximately 100 patients had been treated continuously with clevidipine for a minimum of 18 hours, including at least 50 patients with acute or chronic end-organ injury. In total, 104/117 patients (88.9%) achieved the pre-defined SBP target range in 30 minutes. The study will certainly serve as a supportive role.

The applicant in response to the questions raised has accepted this study’s supportive role (as opposed to a pivotal study status) and has amended the indication claimed for use of clevidipine to the perioperative states only (see below). This is appropriate as a pragmatic approach.

**ECLIPSE studies**
These were three studies that were designed as safety studies but also had efficacy endpoints. They were all open-label studies as the applicant states that it is difficult to maintain the blinding in the operative setting, which is reasonable. The ECLIPSE–NIC study was in the postoperative setting and used nicardipine as an active comparator. The ECLIPSE–SNP and ECLIPSE-NTG were studies in the perioperative setting and used sodium nitroprusside and nitroglycerin as comparators, respectively. The perioperative setting and patients recruited were similar to those outlined in ESCAPE 1, the postoperative setting similar to that of ESCAPE 2. The primary objective of all trials was to establish the safety of clevidipine in the treatment of hypertension, as assessed by comparing the incidences of death, stroke, myocardial infarction (MI) and renal dysfunction. These endpoints were agreed on by an independent committee. All studies used the area under the curve for the systolic blood pressure outside the pre-specified range (AUC\textsubscript{SBP-D}) as a secondary endpoint. In the NIC and NTG trials there is a similar level of dropout between the treatment groups. However, in the SNP trial, substantially more patients dropped out of the trial before receiving treatment in the sodium nitroprusside group. Clevidiprex provided better blood pressure control compared to NTG (AUC\textsubscript{SBP} median 4.14 vs. 8.87 mmHg x min/h, respectively, p=0.0006) and compared to SNP (median 4.37 vs. 10.50 mmHg x min/h, respectively, p=0.0027). Blood pressure control with Clevidiprex and NIC was similar (median 1.76 vs. 1.69 mmHg x min/h, respectively, p=0.8508) in the postoperative setting. The results of the active controlled trials are considered supportive and not pivotal for efficacy. The point estimates and confidence intervals for the relative risk for the main safety outcomes should be provided, to further aid the assessment of risk: benefit. These results in general do support the efficacy of clevidipine, although there are concerns regarding the difference in treatment effect in the peri- and postoperative settings that the applicant should comment on. Furthermore, the hypertension in peri-operative setting is a population where clevidipine has shown efficacy.

The applicant was asked to detail the reasons and rationale behind the broader indication that was initially sought: “Clevidipine is indicated for the reduction of blood pressure when rapid
and predictable control is desired.” The applicant’s approach and discussion in response to questions has been to amend the indication to restrict this to the perioperative states where most data were available and not include specific situations (such as aortic dissection, eclampsia/ pre-eclampsia and pheochromocytoma) in the broad wording. This approach is pragmatic. It should be noted that there are difficulties in conducting clinical trials in these specific situations. It is likely that data will emerge regarding use in these situations in the post-marketing period and the company should be encouraged to make efforts to collect this information prospectively either through observational studies or in a controlled study of severe hypertension.

**Table-7: Summary of operative settings studied in ESCAPE and ECLIPSE**

<table>
<thead>
<tr>
<th>Operative Setting</th>
<th>ESCAPE-1</th>
<th>ESCAPE-2</th>
<th>ECLIPSE-NTG</th>
<th>ECLIPSE-SNP</th>
<th>ECLIPSE-NIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

The response to clevidipine is similar in all peri-operative states (pre-, intra- and postoperative) and any perceived differences in efficacy are likely to be due to the different comparators used (such as nitroglycerine, nitroprusside and nicardipine). From the data provided by the applicant, it is clear that the effect of clevidipine is consistent in both the ESCAPE studies and ECLIPSE studies. The apparent reason for difference in efficacy in the preoperative and postoperative settings is the much stronger results for placebo in the postoperative setting. The additional analysis of the AUC provides reassurance that the effect of clevidipine is consistent across all perioperative settings. It is understandable that clevidipine may not have shown superiority to nicardipine, as they both belong to the same class and the mechanism of action is similar. The ECLIPSE-NIC trial was not designed to demonstrate superiority between two arterio-selective agents and this argument is accepted.

**Table-8: Logistic regression analysis for the clinical outcomes from all ECLIPSE studies**

<table>
<thead>
<tr>
<th>Risk Variable (unit)</th>
<th>P-value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op SBP ≥ 120 mg/dL (yes/no)</td>
<td>&lt;.0001</td>
<td>3.519</td>
<td>2.433</td>
</tr>
<tr>
<td>Surgery duration (hour)</td>
<td>&lt;.0001</td>
<td>1.363</td>
<td>1.158</td>
</tr>
<tr>
<td>Pre-op Hgb (g/dL)</td>
<td>&lt;.0001</td>
<td>0.812</td>
<td>0.740</td>
</tr>
<tr>
<td>AUC in Q4 (yes/no)</td>
<td>0.0123</td>
<td>1.631</td>
<td>1.112</td>
</tr>
<tr>
<td>Screening SBP (mmHg)</td>
<td>0.0156</td>
<td>1.009</td>
<td>1.002</td>
</tr>
<tr>
<td>≥ 2 surgical procedures (yes/no)</td>
<td>0.0215</td>
<td>1.698</td>
<td>1.081</td>
</tr>
</tbody>
</table>

AUC was derived using the SBP range of 95-145 mmHg pre and post-operative and 75-135 mmHg intraoperative.

The currently proposed indication “Cleviprex is indicated for the rapid reduction of blood pressure in the perioperative setting” is the most appropriate wording based on the data available. The main patient population involved in the studies was cardiac surgical patients, who form the highest risk group given the complexity of the patient population and also the
surgical setting, including anticoagulation, multiple co-morbidities, the use of bypass pump and the concomitant medications. If in this population, safety of rapid blood pressure reduction is demonstrated, then it stands to reason that these findings could be extrapolated to other surgical settings. This is based on the fact that for other types of surgery, where the settings are less complex, the greatest risk would arise from poorly controlled blood pressure rather than rapid reduction of BP. The ability of clevidipine to reduce blood pressure is unlikely to be different in different surgical settings as the mechanism of hypertension is essentially similar. Moreover, trials in essential hypertension and severe hypertension settings have shown the blood pressure lowering effect in these settings. The assessor has found no strong reason to suspect the results from cardiac surgical setting cannot be extrapolated to other surgeries. Therefore, the applicant’s argument that results could be extrapolated to other surgical settings is endorsed as there are few scientific arguments to prove the contrary in this application.

IV.5 Clinical safety
The safety of clevidipine is supported by 19 completed clinical studies in healthy volunteers and hypertensive patients (essential, perioperative and severe hypertension) with 1,307 clevidipine-treated hypertensive patients (a total of 1,406 total clevidipine-treated subjects). The overall strategy for safety evaluation included the review of potential pharmacological class effects resulting from the use of an intravenous (IV) dihydropyridine antihypertensive agent, potential vehicle (lipid formulation) effects, and individual clinical study safety outcomes. The studies included:

- Four Phase I studies in a total of 101 unique healthy volunteers to provide PK, PD and safety/tolerability data. One of these studies, a QT/QTc study, was to establish the electrocardiographic safety of clevidipine over 24 hours.
- Nine Phase II studies in 432 patients with essential hypertension (three studies, 95 patients) and perioperative hypertension (six studies, 337 patients). TMC-CLV-06-01 study was in essential hypertension patients during prolonged (≥72 hours) continuous infusion.
- Two Phase III placebo-controlled efficacy trials (ESCAPE) conducted in perioperative hypertension (N=214 cardiac surgery patients).
- Three Phase III active-controlled, open-label, safety studies (ECLIPSE) conducted in perioperative hypertension (N=1,506 cardiac surgery patients; 752 treated with clevidipine and 754 were treated with the comparators nitroglycerine, sodium nitroprusside or nicardipine).
- An uncontrolled Phase III study (VELOCITY) in patients (N=126) with severe hypertension and organ dysfunction treated with clevidipine.

Clevidipine drug exposure represents a broad spectrum of dose ranges (0.05 μg/kg/min to 12.5 μg/kg/min; approximately 0.25 mg/h to 60 mg/h) and duration of continuous use (up to 72 hours) in moderate- and high-risk patients with essential, perioperative or severe hypertension (1,406 total subjects treated with clevidipine and a similar number treated with comparators/placebo). The majority of patients (75%) were managed at infusion rates ≤16 mg/h. However, patients with severe hypertension enrolled in the VELOCITY trial (TMC-CLV-06-02) demonstrated higher dose requirements and over 50% required infusion rates between 8 mg/h and 32 mg/h, consistent with the proposed dose range included in the package insert (2-32 mg/h). The majority of patients received a continuous infusion for <24 hours (N= 1,199) and an additional 93 patients received continuous infusions between 24 and 72 hours. As expected, most patients included in the perioperative hypertension studies received treatment for a few hours (median 4.34 h). Clevidipine drug exposure represents a broad spectrum of dose ranges (0.05-12.5 μg/kg/min [approximately 0.25 mg/h to 60 mg/h])
with the median total dose administered (14.95 mg) equating to 29.90 mL of clevidipine emulsion. The maximum dose delivered in any patient was 1152.70 mg, which represents an infusion rate of 16 mg/h maintained continuously for 72 hours.

Table-9: Summary of clevidipine exposure (hypertensive patients)

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Overall Infusion</th>
<th>On-drug Infusion</th>
<th>Total dose (mg)</th>
<th>Initial rate (mg/h)</th>
<th>Average rate (mg/h)</th>
<th>Maximum rate (mg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1306</td>
<td>1294</td>
<td>1240</td>
<td>1294</td>
<td>1240</td>
<td>1240</td>
</tr>
<tr>
<td>Median</td>
<td>6.44</td>
<td>4.19</td>
<td>14.86</td>
<td>2.00</td>
<td>3.99</td>
<td>8.00</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>1.45, 19.10</td>
<td>0.92, 16.18</td>
<td>3.45, 66.77</td>
<td>1.75, 2.40</td>
<td>2.28, 7.11</td>
<td>3.98, 16.00</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.02, 196.00</td>
<td>0.02, 127.20</td>
<td>0.01, 1152.70</td>
<td>0.02, 52.32</td>
<td>0.15, 46.19</td>
<td>0.15, 60.00</td>
</tr>
</tbody>
</table>

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 was 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. As expected in this population of patients with hypertensive disease, there was a high prevalence of diabetes (31.7%), peripheral vascular disease (12.4%), heart failure (15.3%) and stroke (10.0%). In the Phase III trials there is a fair representation of the elderly or those ≥ 65 years old and nearly 20% were ≥ 75 years of age. One area of difference is in the distribution of ethnicity. In all healthy volunteer studies, the majority were Caucasian males.

The adverse events overall have been classified by the applicant into subclasses for convenience as three of the ECLIPSE studies that were primarily Phase III safety studies for evaluating clevidipine. The subclassification is in addition to the conventional classification as ADRs, serious ADRs, treatment emergent AEs, laboratory events and others. All the listings adopted the conventional principles of reporting as MedDRA/CIOMS, with frequencies estimated from clinical trials within the development programme. Since there are certain categories of AEs that are frequent in the perioperative hypertension population but may only be seen rarely outside of this setting, these were considered best dealt with separately. The investigators were instructed to record ‘expected’ perioperative complications as a separate category from other AEs. Consequently, the AE rates reported in clevidipine and placebo treated patients are considerably lower than expected.

Specific events such as overshoot hypotension, reflex tachycardia, atrial fibrillation, hypovolemia, rebound hypertension and vehicle (Intralipid) related events were analysed separately for ECLIPSE trials and no significant difference was noted between clevidipine and all comparators. In the development programme, a maximum increase in HR of >30% (baseline to 1 hr after initiation of infusion) was noted in 27.6% of the Cleviprex group participants, 38.2% of the comparator group participants and 5.5% of the placebo group participants. There was higher proportion of participants reporting oedema in the comparator group [45.9% (n=385) vs 35.7% (n=466) with clevidipine]. Nitroglycerine (NTG) had the lowest incidence of peripheral oedema at 9%. Regarding the offset of action of clevidipine, the majority of subjects had an up to 20% increase in BP from end to termination to within 1
hour; suggesting that prolonged hypotension post infusion is not a significant issue. Studies in post-operative patients compared clevidipine (n=752) to NTG (n=278), nitroprusside [SNP] (n=283) or nicorandil [NIC] (n=193). No relevant differences were noted between clevidipine and the comparator groups. Some ADRs appear more common with clevidipine, notwithstanding the caveat that these events are frequent in the clinical setting anyhow. They include atrial fibrillation, hypotension, ventricular tachycardia decreased platelet count and atelectasis. The other events were of similar frequency in clevidipine and the comparator group.

Hypotension classified as a vascular disorder was slightly more common (16.9% vs 14.9%; 124 vs 112). There exists a tenuous relationship between occurrence of hypotension and more frequent occurrence of CEC adjudicated events (of any event, death, stroke, MI and renal dysfunction), which is unsurprising but not specific to clevidipine. The differences in the incidence of CEC-adjudicated events between the clevidipine and all comparators groups were not statistically significant (p-values are all greater than 0.05) when controlling the incidence of hypotension, based on the Cochran-Mantel-Haenszel (CMH) test. The significant fact of importance is the rapid onset and offset of action of clevidipine as detailed before. Similarly, although higher percentages of patients with hypotension and atrial fibrillation (AF) and patients with hypotension and ventricular tachycardia were observed in the clevidipine group compared to the all-comparators group (34.3% vs. 32.5% and 8.6% vs. 5.0%, respectively), these differences were also small, not statistically significant and unlikely to be clinically meaningful.

Table-10: Relation between hypotension and VT or AF; clevidipine vs comparators

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Event</th>
<th>Hypotension</th>
<th>Clevidipine n/N (%)</th>
<th>All Comparators n/N (%)</th>
<th>P-value (CMH test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Yes</td>
<td>12/35 (34.3)</td>
<td>13/40 (32.5)</td>
<td>0.3655</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>282/717 (35.1)</td>
<td>239/714 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>Yes</td>
<td>3/35 (8.6)</td>
<td>2/40 (5.0)</td>
<td>0.2725</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>822/717 (11.4)</td>
<td>70/714 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>

In the VELOCITY trial, the listings are limited to >3% incident ADRs and there appear to be few events common to this group with either the perioperative group or with other hypertension trials. The list does not include events such as atrial fibrillation, myocardial infarction, hypotension and tachycardia including supraventricular tachycardia. The low frequency, whilst reassuring, is also surprising. The applicant has alluded to the underreporting of AF in the studies and the action taken in 2004-2005.

There were no significant differences between groups in the mean or median changes in laboratory parameters for creatinine, liver function tests or triglycerides (TG) levels. Within the development programme, there were no reports of adverse clinical effects due to lipid administration and no evidence of increased incidence of infection in clevidipine exposed patients. There was no difference in the incidence of potentially lipid-related AEs (liver dysfunction, pancreatitis, clotting abnormalities and impaired respiratory function) between the groups studied. The changes in median percent blood TG concentrations varied (11.9 to 7.1%) but all were considered clinically insignificant. Of note, the clevidipine group would perforce have had higher TG levels immediately after infusion, purely due to the nature of Intralipid infusion. However, these increases were transient, ill-sustained and without clinical changes or impact. Safety in special populations of interest has been addressed and there
appears no specific risk other than small differences in frequency of increased incidence of elevations of serum creatinine.

The incidence of serious adverse events (SAEs) in patients treated for perioperative hypertension was similar for patients receiving clevidipine (20.3%) and active comparators (21.8%). There were some differences between clevidipine and comparators in the events rates noted in the SAE listing, such as acute renal failure, hypotension, myocardial infarction, ventricular tachycardia and a few others. It is understandable that in the cardiac surgical perioperative setting, a number of these events are frequent, irrespective of the agents used. Based on the characters within each randomised group, there are likely to be small differences in the unadjusted event rates. This has been addressed by using an independent CEC in this development programme. The CEC adjudicated events are likely to be a better representation of events and possibly closer to the truth than investigator reported events that have some disadvantages. In this development programme, this is amply demonstrated by the underreporting of atrial fibrillation and may have occurred with other events as well. The CEC adjudicated events are summarised below:

### Table-11: CEC adjudicated events from ECLIPSE studies

<table>
<thead>
<tr>
<th>Term</th>
<th>Clevidipine (N=752)</th>
<th>All Active Comparators (N=754)</th>
<th>Difference (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CEC-adjudicated event, n (%)</td>
<td>77 (10.7)</td>
<td>86 (11.8)</td>
<td>-1.1 (-4.37, 2.13)</td>
</tr>
<tr>
<td>Death</td>
<td>20 (2.8)</td>
<td>28 (3.8)</td>
<td>-1.1 (-2.90, 0.78)</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (1.1)</td>
<td>12 (1.7)</td>
<td>-0.6 (-0.1, -1.70)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16 (2.3)</td>
<td>17 (2.4)</td>
<td>-0.1 (-1.70, 1.46)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>56 (7.9)</td>
<td>56 (7.9)</td>
<td>0.0 (-2.82, 2.78)</td>
</tr>
</tbody>
</table>

Overall, the CEC adjudicated events are considered a better representation and these did not show a higher risk of events than either the comparator agents or based on the report from Society of Thoracic Surgeons’ dataset (except for MI). Notwithstanding this observation, appropriate information relating to commonly noted SAEs are included in the product literature.

### IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cleviprex 0.5 mg/ml injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimisation activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdose or Unwanted Hypotension</td>
<td>Routine pharmacovigilance&lt;br&gt;Active surveillance of events describing lipid overload and its possible consequences, such as pancreatitis and hepatic, using targeted questions for use by Medical Information and Pharmacovigilance personnel during cell receipt and follow-up with the reporter. Inclusion of discussion of overdose or unwanted hypotension in the PSUR. Using customised searches, signalling of events in the safety database as defined by MedDRA search terms will be used to evaluate any new patterns of overdose or unwanted hypotension events and will occur on a monthly basis.</td>
<td>Proposed risk minimisation activities (routine and additional)&lt;br&gt;The proposed Summary of Product Characteristics contains the following: Section 4.4 Special warnings and precautions for use warns that &quot;Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia&quot;, which details that &quot;Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia. If either occurs with Clevidipex, decrease the dose.&quot; Section 4.2 Pharmacology and method of administration states &quot;Titrates drug to achieve the desired blood pressure reduction. Individualise dosage depending on the blood pressure to be attained and the response of the patient.&quot;</td>
</tr>
<tr>
<td>Reflex Tachycardia</td>
<td>Routine pharmacovigilance in addition to:&lt;br&gt;Active surveillance of reflex tachycardia events including the use of targeted questions for use by Medical Information and Pharmacovigilance personnel during cell receipt and follow-up with the reporter. Inclusion of discussion of reflex tachycardia in the PSUR. Using customised searches, signalling of events in the safety database as defined by MedDRA search terms will be used to evaluate any new patterns of reflex tachycardia events and will occur on a monthly basis.</td>
<td>Proposed risk minimisation activities (routine and additional)</td>
</tr>
<tr>
<td>Potential Risk</td>
<td>Proposed risk minimisation activities (routine and additional)</td>
<td></td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>Routine pharmacovigilance in addition to:&lt;br&gt;Active surveillance of nosocomial or hospital-acquired infections including the use of targeted question for use by Medical Information and Pharmacovigilance personnel during cell receipt and follow-up with the reporter. Inclusion of discussion of nosocomial or hospital-acquired infections in the PSUR. Using customised searches, signalling of events in the safety database as defined by MedDRA search terms will be used to evaluate any new patterns of nosocomial or hospital-acquired infection events and will occur on a monthly basis.</td>
<td>The proposed Summary of Product Characteristics contains the following:&lt;br&gt;Section 4.4 Special warnings and precautions for use warns that &quot;Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia&quot;, which details that &quot;Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia. If either occurs with Clevidipex, decrease the dose.&quot; Section 4.9 Undesirable effects states that &quot;Failure to practice appropriate aseptic technique may lead to contamination of infused product and the potential for systemic infection.&quot; Section 4.4 Special warnings and precautions for use. Instructions for Administration states that &quot;Strict aseptic technique must be maintained while handling Clevidipex. Clevidipex is a single-use parenteral product that contains phospholipids and can support the growth of microorganisms. Do not use if contamination is suspected. Once the stopper is punctured, use within 12 hours and discard any unused portion.&quot;</td>
</tr>
<tr>
<td>Lipid Overload (hyperglycemia and pancreatitis)</td>
<td>Routine pharmacovigilance in addition to:&lt;br&gt;Active surveillance of events describing lipid overload including the use of targeted questions for use by Medical Information and Pharmacovigilance personnel during cell receipt and follow-up with the reporter. Inclusion of discussion of Lipid overload in the PSUR. Using customised searches, signalling of events in the safety database as defined by MedDRA search terms will be used to evaluate any new patterns of events describing lipid overload and will occur on a monthly basis.</td>
<td>Proposed risk minimisation activities (routine and additional)</td>
</tr>
<tr>
<td>Missing Information</td>
<td>Proposed risk minimisation activities (routine and additional)</td>
<td></td>
</tr>
<tr>
<td>Exposure to clevidipine during pregnancy and lactation</td>
<td>Routine pharmacovigilance is planned, including active follow-up on all reports received of exposure to clevidipine in pregnant or lactating women Ongoing AE report surveillance for pregnant and lactating patients</td>
<td>No known exposure in this key patient group has occurred. Ongoing surveillance and report analysis is regarded as the most effective way to obtain AE data in these patients</td>
</tr>
<tr>
<td>Use of clevidipine in pediatric populations</td>
<td>Routine pharmacovigilance is planned, including active monitoring and ongoing AE report surveillance for indications and clinical circumstances of AEs in pediatric patients</td>
<td>No known exposure in this key patient group has occurred. Ongoing surveillance and report analysis is regarded as the most effective way to obtain AE data in these patients</td>
</tr>
</tbody>
</table>
IV.7  Discussion on the clinical aspects

The efficacy of clevidipine has been demonstrated in the preoperative hypertensive population in comparison to placebo in two studies. Clevidipine reduces SBP, MAP and DBP in a dose dependent manner with rapid onset of action and reasonably rapid offset.

The pharmacokinetics of the product have been studied in relevant populations and there are no major concerns relating to this. Drug interactions were not studied in detail, but there is sufficient logic to accept the applicant’s arguments. An effect has been shown in essential hypertension population in terms of reduction of blood pressure, although this does not necessarily fit the “urgent need for therapy” group. In the severely hypertensive population, again an effect has been shown in an uncontrolled open label study that provides no comparator either for ability to reduce BP in relative terms or in terms of benefit in clinical events. The active controlled studies in peri-operative patients, ECLIPSE studies do provide valuable input in terms of efficacy and safety (these were primarily safety studies) in comparison to three reasonably commonly deployed agents: nitroprusside, nitroglycerine and nicardipine. Inevitably these were open studies and the design has been adequately justified by the applicant based on difficulties in performing double dummy designs in the context of the use of these agents and the Intralipid infusion. This is reasonable and acceptable.

Safety studies adequately demonstrate that the risk of clevidipine is not greater than the comparators in the ECLIPSE studies. The overall adverse event rates are not onerous. The applicant has analysed the data for relation between hypotension and arrhythmia and, whilst the frequency of events was numerically greater in those who experienced hypotension, this was not specific to clevidipine and there was no statistically significant difference between all comparators and clevidipine. This is reassuring to an extent but these relations are also evaluated as part of the observational study proposed in the RMP. The exclusion of certain populations that could be at risk (left bundle branch block and permanent ventricular pacing) is supported. Absence of interaction studies has been explained and is acceptable.

There are no objections to the approval of Cleviprex 0.5 mg/ml emulsion for injection from a clinical point of view.

V  User consultation

The patient information leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
VI  Overall conclusion, benefit/risk assessment and recommendation

Quality
The important quality characteristics of Cleviprex 0.5 mg/ml emulsion for injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

Non-clinical
Adequate justification has been provided for the absence of certain specific safety pharmacology studies, as the end-points have been covered in other toxicity studies.

No issues arise from the pharmacokinetics of clevidipine. Clevidipine is rapidly hydrolysed to form formaldehyde and metabolite M1, and the formaldehyde is responsible for the positive effects in some in vitro genotoxicity assays. However, the quantities of formaldehyde generated are lower than endogenous levels and are rapidly detoxified in vivo.

The toxicity of clevidipine has been adequately investigated in appropriate species (rats and dogs). Reproductive toxicity studies have shown effects on embryo-fetal development and parturition that are typical of calcium channel blockers.

Clevidipine is not considered to pose a risk to the environment.

The non-clinical data support the proposed dose and indication.

Efficacy
Efficacy of clevidipine has been demonstrated in preoperative hypertensive population in comparison to placebo in two studies. Clevidipine reduces SBP, MAP and DBP in a dose-dependent manner with rapid onset of action and reasonably rapid offset.

The pharmacokinetics of clevidipine have been studied in relevant populations and there are no major concerns relating to this.

Drug interactions were not studied in detail but there is sufficient logic to accept the applicant’s arguments.

The active controlled studies in perioperative patients provide valuable input in terms of efficacy and safety (these were primarily safety studies) in comparison to three reasonably commonly deployed agents; nitroprusside, nitroglycerine and nicardipine.

Safety
Safety studies adequately demonstrate that the risk of clevidipine is not greater than the comparators. The overall adverse event rates are not onerous.

The SmPC and PIL are satisfactory and contain appropriate statements regarding the safety of clevidipine. Satisfactory product labelling has also been submitted.

Benefit-risk assessment
The benefit-risk ratio for this product is considered to be acceptable. A Marketing Authorisation should be granted.
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in-line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK version of the SmPC and PIL for this product is available on the MHRA website.

The approved label mock-ups are shown below:
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To submit the ACCELERATE clinical study report, following a commitment made during the initial decentralised procedure.</td>
<td>PL 16881/0003 – 0013 UK/H/2477/001/II/005</td>
<td>SmPC and PIL</td>
<td>30 June 2014</td>
<td>17 December 2014</td>
<td>Approved</td>
<td>Y (Annex I)</td>
</tr>
<tr>
<td>To update section 5.1 of the SPC with new information regarding possible rebound hypertension following clevidipine discontinuation.</td>
<td>PL 16881/0003 – 0024 UK/H/2477/001/II/013</td>
<td>SmPC</td>
<td>07 January 2016</td>
<td>07 March 2016</td>
<td>Approved</td>
<td>Y (Annex II)</td>
</tr>
<tr>
<td>To update section 6.6 (Disposal) of the SmPC to add new compatible fluids. Consequentially the PIL has been updated.</td>
<td>PL 16881/0003 – 0026 UK/H/2477/001/II/011</td>
<td>SmPC and PIL</td>
<td>07 January 2016</td>
<td>07 March 2016</td>
<td>Approved</td>
<td>Y (Annex III)</td>
</tr>
<tr>
<td>To update section 4.2 of the SPC to change recommendations for maximum daily volume of infusion.</td>
<td>PL 16881/0003 – 0027 UK/H/2477/001/II/010</td>
<td>SmPC</td>
<td>07 January 2016</td>
<td>07 March 2016</td>
<td>Approved</td>
<td>Y (Annex IV)</td>
</tr>
</tbody>
</table>
Annex I

Reference: PL 16881/0003 – 0013
Product: Cleviprex 0.5 mg/ml emulsion for injection
Active Ingredients: Clevidipine

Reason:
To submit the ACCELERATE clinical study report following a commitment made during the initial marketing authorisation application (MAA) decentralised procedure. Consequential updates to sections 4.8 and 5.1 of the SmPC and the PIL have been made.

Background
During the initial decentralised procedure (DCP) for this licence the following point was received from the CMS Germany:

A recent cerebrovascular accident CVA (within 3 month of screening) was an exclusion criterion in the two ESCAPE studies. Therefore, a warning in the SmPC and PIL about lack of data is proposed. Additionally, the MAH should commit to collect additional data from post marketing specific studies in this subgroup.

In the response to this point, the applicant stated that this was an exclusion criterion because the original studies were those in patients requiring surgery in which CVA would constitute a large risk for surgery and would thus be a confounding factor. The applicant confirmed that a Phase IIIb pilot study (the ACCELERATE study) had been performed to examine the blood pressure response to clevidipine in 35 patients with acute intracerebral haemorrhage (ICH). As the study report had not been finalised at the time, a commitment was made to submit the report as a variation, after completion of the DCP.

Additionally, a clinical study report for the PRONTO study was available and the marketing authorisation holder (MAH) included this in the submission.

Supporting Evidence

EFFICACY DATA

- **ACCELERATE study design:**
The trial was designed as a single-arm, open-label dose titration efficacy and safety trial, in patients presenting with a systolic blood pressure (SBP) >160 mmHg and computed tomography-confirmed intracerebral haemorrhage (ICH), within 12 hours of symptom onset.

The primary objective was to evaluate the efficacy of a titration dosing regimen. Secondary objectives included evaluation of the number of patients who reached the target systolic blood pressure (SBP) within 30 minutes of the initiation of treatment, blood pressure (BP) management within the target range, the need for alternative antihypertensive agents and the mean and median dose of clevidipine administered and safety of a prolonged infusion of clevidipine.

Clevidipine was infused at an initial rate of 2 mg/h for at least 1.5 minutes, and thereafter titrated to effect in order to reduce SBP to the target range (≥140 mmHg to ≤160 mmHg). The protocol specified that the infusion rate must be at least 1.0 mg/h and must not exceed...
32.0 mg/h. During the initial 30 minutes of the treatment period, clevidipine was to be administered as monotherapy whenever possible and the use of alternative antihypertensive agents was limited to medical necessity as determined by the investigator. After the first 30 minutes of clevidipine treatment, clevidipine could be continued up to a maximum of 96 hours. Patients were transitioned to oral antihypertensive therapy as required, approximately one hour prior to cessation of the clevidipine infusion.

A total of 37 patients were enrolled into the study. Patients had a median age of 64 years, mean baseline SBP of 186 mm Hg and a mean diastolic blood pressure (DBP) of 85 mm Hg.

- **ACCELERATE study results**

The modified intent to treat population consisted of 33 patients. The primary endpoint of this study was the median time to achieve target BP (SBP ≤160 mmHg to ≥140 mm Hg) within 30 minutes of initiation of the clevidipine infusion.

The secondary efficacy endpoints of the study were:

- The percentage of patients who reached a SBP of ≤160 mmHg within 30 minutes of initiation of the clevidipine infusion
- Percent change from baseline in SBP during the initial 30 minutes of clevidipine infusion
- Magnitude, frequency and duration of SBP excursions (calculated as AUC) outside the target range normalized per hour for the duration of the clevidipine monotherapy infusion
- Percent time BPs were maintained within the target range (SBP ≤160 mm Hg to ≥140 mmHg) over each 24 hours during monotherapy infusion of clevidipine
- Mean and median dose of clevidipine during the treatment period
- The addition of an alternative antihypertensive agent(s) with or without clevidipine

Intravenous (IV) clevidipine was rapidly effective for management of BP in this study of ICH patients with acute hypertension. The median time to achieve the target SBP range of ≤160 mm Hg to ≥140 mm Hg was 5.5 minutes.

Thirty-two of 33 patients (97%) had SBP ≤160 mm Hg within the first 30 minutes after initiation of clevidipine infusion and before receiving additional or alternative antihypertensive agents. SBP decreased by a median of 6.0 mm Hg (3.6%) at 3 minutes after the initiation of clevidipine infusion, and decreased by a median of 36.0 mm Hg (18.9%) at 30 minutes after the initiation of clevidipine infusion.

All but one patient remained on clevidipine monotherapy without additional or alternative antihypertensives for hypertension for the first 30 minutes of treatment with clevidipine.

- **PRONTO study design**

This was an open label, randomised pilot study designed to investigate the efficacy and safety of early intervention with clevidipine for the treatment of hypertension in patients presenting with acute heart failure (AHF).

The primary objective was to evaluate the efficacy of an IV infusion of clevidipine as compared with standard of care IV antihypertensive therapy in reducing BP in patients with hypertensive AHF. The secondary objectives were to evaluate the safety and further evaluate the efficacy of clevidipine as compared with standard of care. Exploratory objectives evaluated the effects on fluid balance, diuretic use and renal function.
Treatment was randomised (1:1) to balance patient demographics and baseline characteristics. In the clevidipine group, the study drug was administered via IV infusion, at a starting dose of 2 mg/h for 3 minutes and thereafter titrated to the desired SBP within a pre-specified target range as determined by the investigator. The maximum infusion rate was not to exceed 32 mg/h and the minimum infusion rate was not to be lower than 1 mg/h. It was intended that clevidipine should be administered as monotherapy for the first 30 minutes, and the use of alternative antihypertensive agents was discouraged and limited to medical necessity. Clevidipine infusion could be administered continuously for a maximum duration of 96 hours. In the standard of care group, patients received an IV antihypertensive agent according to the institution’s treatment practice, and treatment could continue beyond 96 hours if medically warranted. Following the treatment period with clevidipine or standard of care, patients could be transitioned to an oral antihypertensive medication as necessary.

- **PRONTO study results**
The setting was the treatment of non-perioperative hypertension in patients presenting with acute heart failure, which is not relevant to the licenced indications. For this reason the data was only assessed from a safety, and not an efficacy point-of-view.

**SAFETY DATA**

- **Exposure**
ACCELERATE study: The safety population comprised 35 patients (27 male and 8 female patients with an average age of 63.5±12 years) who were treated with clevidipine. This population included 7 patients who had intracranial pressure (ICP) monitoring at enrolment. Of the 35 patients in the safety population, 28 completed, and 7 patients did not complete the study. Of the seven patients that did not complete the study, 2 patients who received clevidipine were subsequently determined to be ineligible for the study, 2 patients were lost to follow-up, 2 patients died and 1 patient was transferred away from the study site.

PRONTO study: The safety population comprised 104 patients; 51 received clevidipine and 53 received standard of care (nitroglycerin (n=30), nicardipine (n=16), IV isosorbide dinitrate (n=4), nitroprusside (n=1), hydrazine (n=1) and diltiazem (n=1)).

- **Dosing**
In the ACCELERATE study, patients in the safety population were exposed to clevidipine infusion for a median duration of 20 hours, excluding time intervals at which the infusion was stopped temporarily. The mean and median total doses infused were 260 mg and 116 mg respectively.
In the PRONTO study the mean total dose of clevidipine infused was 31 mg.

- **Overview of ADRs**
Common adverse events (AEs) reported in both studies and their frequencies were generally consistent with previous clinical experience with IV clevidipine infusion.
In ACCELERATE, the median percent change from baseline in heart rate (HR) (pre-specified safety endpoint) was no greater than 4.9% for all patients (n=35), and 6.4% for patients with ICP monitoring (n=7) receiving BP reduction. Also in this study, no patients had SBP less than 90 mm Hg for the first 30 minutes of clevidipine therapy; 1 patient had SBP less than 90 mm Hg after the first 30-minute treatment period.

The common TEAEs are provided in the tables below:
ACCELERATE (TEAEs reported in ≥5% of all patients, safety population)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All patients (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Agitation</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Hypophosphataemia</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Brain oedema</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Prothrombin time prolonged</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Rhonchi</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>White blood cell count increased</td>
<td>2 (5.7)</td>
</tr>
</tbody>
</table>

PRONTO (TEAEs reported in ≥2 of all patients, safety population)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Clevidipine N=51 n(%)</th>
<th>Standard of Care IV therapy N=53 n(%)</th>
<th>All patients N=104 n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11 (21.6)</td>
<td>13 (24.5)</td>
<td>24 (23.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (11.8)</td>
<td>6 (11.3)</td>
<td>12 (11.5)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>5 (9.8)</td>
<td>2 (3.8)</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (2.0)</td>
<td>3 (5.7)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>2 (3.9)</td>
<td>1 (1.9)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (2.0)</td>
<td>2 (3.8)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (2.0)</td>
<td>2 (3.8)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (3.9)</td>
<td>1 (1.9)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (5.9)</td>
<td>0 (0.0)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>2 (3.9)</td>
<td>1 (1.9)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (3.9)</td>
<td>1 (1.9)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (3.9)</td>
<td>1 (1.9)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Anthralgia</td>
<td>2 (3.9)</td>
<td>0 (0.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>2 (3.9)</td>
<td>0 (0.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>2 (3.9)</td>
<td>0 (0.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (3.9)</td>
<td>0 (0.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0 (0.0)</td>
<td>2 (3.8)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>2 (3.9)</td>
<td>0 (0.0)</td>
<td>2 (1.9)</td>
</tr>
</tbody>
</table>
- **Serious adverse events (SAEs) and deaths**

Two deaths occurred during the ACCELERATE study; one in a patient with an SAE of worsening ICH (assessed as unlikely to be related to clevidipine) and the other in a patient with a SAE of cardiopulmonary arrest (assessed as unrelated to clevidipine). Five deaths were reported during the PRONTO study, three in the clevidipine group and two in the SOC group, all of which were considered unrelated to study drugs.

Nine patients (25.7%) had at least one SAE during the ACCELERATE study. All SAEs were assessed as unrelated or unlikely related to the study drug. One patient discontinued clevidipine treatment due to an AE (hypotension). The patient had episodes of hypotension, starting with a blood pressure of 82/47 mmHg, and assessed as non-serious, moderate in severity and definitely related to study treatment. The AE had a duration of 51 minutes and was reported to be resolved 29 minutes after study drug was discontinued. There were a higher percentage of patients reported to have SAEs in the ICP-monitored subgroup, as might be expected due to the more severe underlying medical conditions.

In the PRONTO study, a total of 37 SAEs were reported in 22 patients, with no apparent differences or clear trends between treatment groups. None of the SAEs were considered related to study treatment. One patient discontinued clevidipine due to an AE (myalgia), which was mild in nature and considered definitely related to the study drug. The patient recovered and the event was resolved within two hours of symptom onset.

- **Laboratory findings**

In both trials, laboratory results were consistent with the known safety profile of clevidipine.

**Evaluation of efficacy data**

The ACCELERATE study was a small, uncontrolled and open-label trial in a patient population differing from that indicated for Cleviprex, but generally of an appropriate design, conduct and analysis. Although the study was not undertaken specifically in the perioperative setting, a brief description of the ACCELERATE study in the SPC is relevant to neurosurgical patients. Whilst the study does not cover patients with thromboembolic CVA, the experience in acute intracerebral haemorrhage is of interest to the prescriber as recent CVA (within 3 months of screening) was an exclusion criterion in the two ESCAPE studies.

The submission of the results of the PRONTO study was not part of the licensing commitment. The safety data from this study are assessed but the study population of hypertensive heart failure is not relevant to the licenced indication from an efficacy point of view and, therefore, will not be assessed in this variation. It should also be noted that the use of calcium channel blockers in the setting of heart failure is not endorsed in the current ESC guidelines.

**Evaluation of safety data**

In the MAA it was noted that recent CVA (within 3 months of screening) was an exclusion criterion in the two ESCAPE studies, and that the MAH should commit to collect additional data from specific post marketing studies in this subgroup. This includes the ACCELERATE trial now presented in this variation.

The applicant also submits results from the PRONTO study. Both studies were in the non-perioperative setting, but had the same starting and maximum infusion dose. Notably these data include patients infused for a prolonged period of time. There are no significant new safety signals in either study, AEs being generally consistent with the known safety profile.
Clearly, the uncontrolled nature of the ACCELERATE trial and the open-label nature of both studies confounds full interpretation, for example headache, vomiting and agitation seen in the ACCELERATE trial could clearly be due to the presenting intracerebral haemorrhage.

**Overall conclusions**

The follow-up commitment to submit the results of the ACCELERATE study has been completed.

The new data does not adversely affect the risk: benefit of the product in the current licenced indications.

Sections 4.8 and 5.1 of the SmPC and Section 4 of the PIL have been updated accordingly.

The current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The variation is recommended for approval.

**Decision** - **Granted**

**Date** - **17 December 2014**
Annex II

Reference: PL 16881/0003 – 0024
Product: Cleviprex 0.5 mg/ml emulsion for injection
Active Ingredients: Clevidipine

Reason:
To update section 5.1 of the SmPC with new information regarding possible rebound hypertension following clevidipine discontinuation.

Background:
The applicant proposes to revise the following text to the Pharmacodynamic section of the SmPC as follows:

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 of continuous infusion, in patients that were not transitioned to other antihypertensive therapies, there was some evidence of rebound hypertension following clevidipine discontinuation.

Supporting Evidence:
The applicant justifies this change as follows:

There were no reports of rebound hypertension in any of the clinical studies in association with clevidipine or comparator treatment; however, as with other oral and IV antihypertensives there is a theoretical possibility that it will occur.

A similar conclusion resulted from the FDA analysis of data from a study that was conducted during the Cleviprex NDA review. The FDA used a different method to the protocol’s prespecified analysis. In the FDA analysis, the data beyond the 4 hour time period post study drug administration, and patients who were started on concomitant medications at 4 hours post study drug discontinuation, were excluded.

The sponsor’s prespecified analysis included all patients. To assure that analyses were not biased by concomitant medications, the protocol prospectively specified that the analyses of possible rebound hypertension would be conducted using the 4-hour time period immediately following the termination of study drug infusion, based on the rapid clearance and offset of clevidipine blood pressure lowering effects (5-15 minutes).

Compared to the sponsor’s analysis that included all subjects the following was established by the second FDA analysis:

1. Rebound dose-response is gone.
2. 2 mg/hr effect is now significant and the mean estimate is doubled.
3. From 76 hours to 80 hours there is a trend showing blood pressure rise in all dose groups.
4. The 8 mg/hr dose also shows a rise in SBP from 76 to 80 hour from a value below that of placebo with different “n”s from the sponsor’s analysis.
5. No rebound at 76 hours (4 hr post study-drug administration termination).
6. Hr 80 (8 hr post study-drug administration termination) remains the worse.
As a result of the review of this data, the MAH accepts that there is at least some evidence of rebound hypertension in those patients who are not transitioned to oral antihypertensives upon discontinuation of clevidipine. Therefore, the MAH has adopted the appropriate language in the Company Core Data Sheet (CCDS) and proposes to update the SmPC as a consequence.

**Evaluation:**
The current SmPC already states in section 4.2 that patients who receive prolonged clevidipine infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after infusion is stopped.

For the purposes of harmonising their CCDS the applicant wishes to clarify the statement in section 5.1, in line with the US SmPC.

**Conclusion:**
The new information does not significantly affect the risk: benefit and is clinically acceptable.

No change to the PIL has been applied, and none is required.

The current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The variation is recommended for approval.

**Decision** - Granted
**Date** - 07 March 2016
Annex III

Reference: PL 16881/0003 – 0026
Product: Cleviprex 0.5 mg/ml emulsion for injection
Active Ingredients: Clevidipine

Reason:
To update section 6.6 (Disposal) of the SmPC to add new compatible fluids. Consequentially the PIL has been updated.

Background:
The applicant proposes to update the list in Section 6.6 of the SmPC to include 0.45% Sodium Chloride, and 40 meq Potassium Chloride in 0.9% Sodium Chloride and to update the corresponding text in the Healthcare Professional’s section of the PIL accordingly.

Supporting Evidence:
Cleviprex should not be diluted or administered in the same line as other parenteral products or solutions. However, in a comprehensive study, the physical compatibility of a 1:1 mixture of Cleviprex with parenteral fluids and drug products commonly used in the same hospital settings was evaluated, as a surrogate for Y-site injection.

The physical characteristics that are critical to the physico-chemical stability of Cleviprex were evaluated upon mixing and after storage at room temperature (approximately 23±2°C):

During these studies, Cleviprex was found to be physically compatible when admixed if there was no significant change in any of these characteristics.

Evaluation:
Valid data were presented which justify the inclusion of the additional parenteral fluids proposed.

No chemical compatibility data are presented. Chemical compatibility data between 0.45% Sodium Chloride and clevidipine have not been reported and are not required.

Lactated Ringer’s Solution, already approved for co-administration with clevidipine, contains potassium, albeit at a reduced level (4meq/L). Consequently the RMS is satisfied that there is negligible risk of chemical incompatibility between 40 meq Potassium Chloride in 0.9% Sodium Chloride and clevidipine.

Conclusion:
The proposed change to the SmPC and PIL is acceptable.

The current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The variation is recommended for approval.

Decision - Granted
Date - 07 March 2016
Reason:
To update section 4.2 of the SmPC to change recommendations for maximum daily volume of infusion. Consequentially the PIL has been updated.

Background:
The posology and administration section of the currently approved SmPC states that no more than 1000 ml of Cleviprex should be infused in the initial 24-hour period. However, the SmPC does not comment on the amount of lipid emulsion that can be infused in any subsequent period. The applicant proposes to clarify this text to state that no more than 1000 ml of Cleviprex is infused in any 24-hour period:

No more than 1000 mL of clevidipine infusion is recommended in the initial 24-hour period due to the associated lipid load.

Supporting Evidence:
Clevidipine is formulated as a lipid emulsion in 20% soybean oil, composition similar to Intralipid, a fat emulsion used widely in parenteral nutrition.

The MAH notes that 1000ml of Cleviprex contains approximately 200 g of lipid, equivalent to the maximum recommended daily dose for Intralipid 20% (2.5 g of fat/kg of body weight) assuming an 80 kg patient (Intralipid US Prescribing Information, 2000)

The UK intralipid 20% prescribing information (national licence) allows a maximum of 3g/kg body weight in 24 hours.

One of the cited references notes that the amount of lipid should be restricted further in order to avoid adverse effects, eg 0.8 to 1.5g/kg/day in patients with acute pancreatitis - however Cleviprex is contraindicated in acute pancreatitis if accompanied by hyperlipidaemia, as well as in other patients with severe hyperlipidaemia.

Evaluation:
Section 4.2 of the SmPC already notes that 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 clevidipine formulation.

This change is more of a clarification, the existing text did not exclude multiple separate infusions. It is possible that clevidiprex might be used more than once over the short term if a patient has several anaesthetic procedures - taking into account that the average duration of infusion will be only a few hours, the risk:benefit context and the safety margin for overall lipid load discussed, there are no clinical concerns and this addition to the SmPC is accepted.

No change to the PIL has been applied, and none is required.
Conclusion:
The proposed change to the SmPC is acceptable.

The current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The variation is recommended for approval.

<table>
<thead>
<tr>
<th>Decision</th>
<th>-</th>
<th>Granted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>-</td>
<td>07 March 2016</td>
</tr>
</tbody>
</table>