AUSTRALIAN PRODUCT INFORMATION - CLEVIPREX® (CLEVIDIPINE)

1. NAME OF THE MEDICINE

Clevidipine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

Cleviprex is a sterile, milky-white opaque emulsion containing 0.5 mg/mL of clevidipine. For the full list of excipients see section 6.1.

Cleviprex has a pH of 6.0 – 8.0 and is a ready-to-use emulsion.

3. PHARMACEUTICAL FORM

Injectable emulsion.
Milky-white opaque emulsion.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

DOSAGE

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

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

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

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

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

Adults/Elderly population

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

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

METHOD OF ADMINISTRATION

Cleviprex is for single use in one patient only. Strict aseptic technique must be maintained while handling Cleviprex. Cleviprex is a single-use parenteral product that contains phospholipids and can support the growth of micro organisms. Do not use if contamination is suspected. Once spiked, begin infusion immediately. Use within 12 hours and discard any unused portion.

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

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

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

Protection from light during administration is not required.

Cleviprex should not be diluted.

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

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

MONITORING

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

Special populations

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

Paediatric population

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

Patients on other lipid-based therapies

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

4.3 CONTRAINDICATIONS

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

Defective lipid metabolism

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

Severe aortic stenosis

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Use strict aseptic technique. Once spiked, begin infusion immediately. Use within 12 hours and discard any unused portion.

IDENTIFIED PRECAUTIONS

Hypotension and reflex tachycardia

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

Negative Inotropy

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

Beta-blocker withdrawal

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

Rebound Hypertension

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

Pheochromocytoma

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

USE IN THE ELDERLY

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

PAEDIATRIC USE

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

EFFECTS ON LABORATORY TESTS

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

EFFECTS ON FERTILITY

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

USE IN PREGNANCY

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

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

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

USE IN LACTATION

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Cleviprex has been evaluated for safety in 19 completed studies, with 99 healthy subjects and 1307 hypertensive patients who received at least one dose of clevidipine (1406 total exposures).

Clevidipine was evaluated in 15 studies in hypertensive patients: 1099 patients with perioperative hypertension, 126 with severe hypertension and 82 patients with essential hypertension.

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

Perioperative Hypertension

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

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

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

	ESCAPE - 1		**ESCAPE - 2**	
	Clevidipine (N=53) n (%)	**Placebo (N=51) n (%)**	**Clevidipine (N=61) n (%)**	**Placebo (N=49) n (%)**
Patients with at least one TEAE	**38 (71.7)**	**33 (64.7)**	**39 (63.9)**	**28 (57.1)**
Cardiac disorders	**14 (26.4)**	**20 (39.2)**	**20 (32.8)**	**13 (26.5)**
Atrial fibrillation	7 (13.2)	6 (11.8)	13 (21.3)	6 (12.2)
Ventricular tachycardia	2 (3.8)	4 (7.8)	4 (6.6)	2 (4.1)
Tachycardia	2 (3.8)	0 (0.0)	1 (1.6)	4 (8.2)
Ventricular extrasystoles	1 (1.9)	0 (0.0)	3 (4.9)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)
General disorders and administration site conditions	**14 (26.4)**	**8 (15.7)**	**16 (26.2)**	**11 (22.4)**
Pyrexia	10 (18.9)	7 (13.7)	3 (4.9)	3 (6.1)
Oedema peripheral	0 (0.0)	1 (2.0)	4 (6.6)	2 (4.1)
Secretion discharge	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**13 (24.5)**	**9 (17.6)**	**15 (24.6)**	**11 (22.4)**
Atelectasis	3 (5.7)	0 (0.0)	2 (3.3)	5 (10.2)
Pulmonary oedema	2 (3.8)	0 (0.0)	1 (1.6)	4 (8.2)

Wheezing	0 (0.0)	0 (0.0)	4 (6.6)	2 (4.1)
Dyspnoea	0 (0.0)	0 (0.0)	3 (4.9)	0 (0.0)
Psychiatric disorders	**10 (18.9)**	**2 (3.9)**	**15 (24.6)**	**10 (20.4)**
Anxiety	3 (5.7)	1 (2.0)	5 (8.2)	3 (6.1)
Restlessness	2 (3.8)	0 (0.0)	2 (3.3)	0 (0.0)
Disorientation	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	1 (1.9)	1 (2.0)	7 (11.5)	3 (6.1)
Renal and urinary disorders	**7 (13.2)**	**4 (7.8)**	**4 (6.6)**	**4 (8.2)**
Renal failure acute	5 (9.4)	1 (2.0)	0 (0.0)	0 (0.0)
Renal insufficiency	0 (0.0)	2 (3.9)	2 (3.3)	0 (0.0)
Infections and infestations	**7 (13.2)**	**1 (2.0)**	**3 (4.9)**	**1 (2.0)**
Pneumonia	2 (3.8)	0 (0.0)	2 (3.3)	0 (0.0)
Gastrointestinal disorders	**6 (11.3)**	**8 (15.7)**	**17 (27.9)**	**12 (24.5)**
Nausea	3 (5.7)	5 (9.8)	13 (21.3)	6 (12.2)
Constipation	2 (3.8)	1 (2.0)	6 (9.8)	3 (6.1)
Blood and lymphatic system disorders	**6 (11.3)**	**5 (9.8)**	**5 (8.2)**	**3 (6.1)**
Nervous system disorders	**6 (11.3)**	**2 (3.9)**	**2 (3.3)**	**4 (8.2)**
Headache	3 (5.7)	1 (2.0)	1 (1.6)	2 (4.1)
Cerebrovascular accident	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (1.9)	1 (2.0)	2 (3.3)	0 (0.0)
Vascular disorders	**5 (9.4)**	**3 (5.9)**	**3 (4.9)**	**1 (2.0)**
Hypotension	3 (5.7)	1 (2.0)	1 (1.6)	0 (0.0)
Troponin increased	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**1 (1.9)**	**1 (2.0)**	**2 (3.3)**	**0 (0.0)**

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

Table 2. Primary endpoint data for the ECLIPSE trials

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

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

Serious Adverse Events and Discontinuation – Perioperative Hypertension Studies

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

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

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

Table 3. Adverse drug reactions in perioperative hypertension patients

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

Table 4. Adverse drug reactions in essential hypertension patients

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

Severe Hypertension

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

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

Less Common Adverse Events in Patients with Severe or Essential Hypertension

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

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

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

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

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

REPORTING SUSPECTED ADVERSE EFFECTS

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

MECHANISM OF ACTION

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

Pharmacodynamic effects

Cleviprex is titrated to achieve the desired reduction in blood pressure. In the perioperative patient population, Cleviprex produces a 4-5% reduction in systolic blood pressure (SBP) within 2-4 minutes after starting a 0.4 mcg/kg/min infusion (approximately 1-2 mg/h). In studies of up to 72 hours there was no evidence of tolerance.

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

Haemodynamics

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

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

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

CLINICAL TRIALS

Perioperative Hypertension

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

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

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

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

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

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

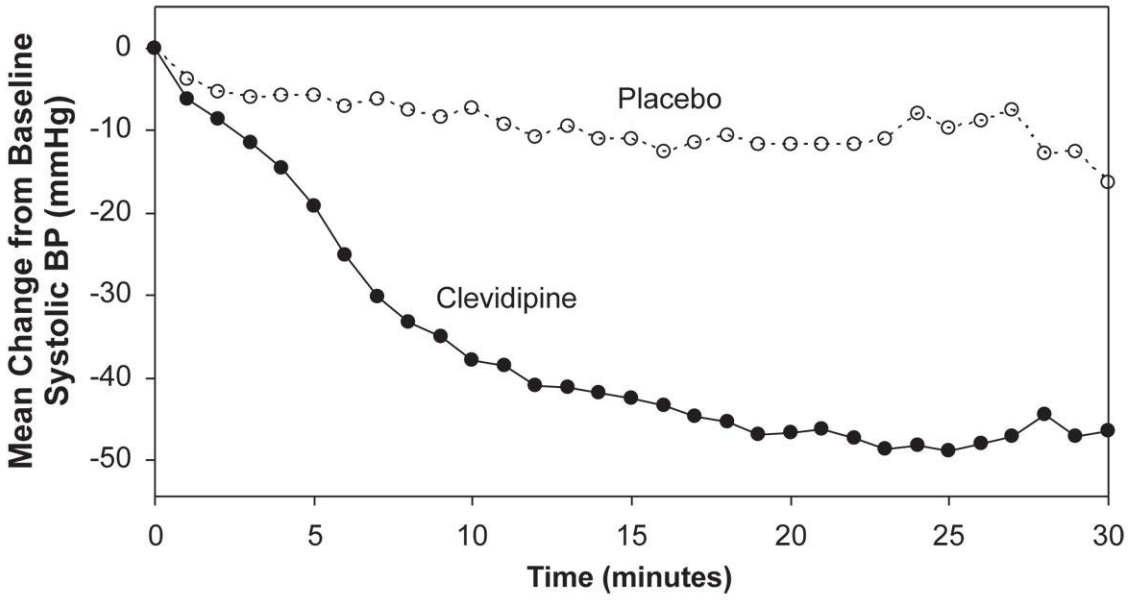
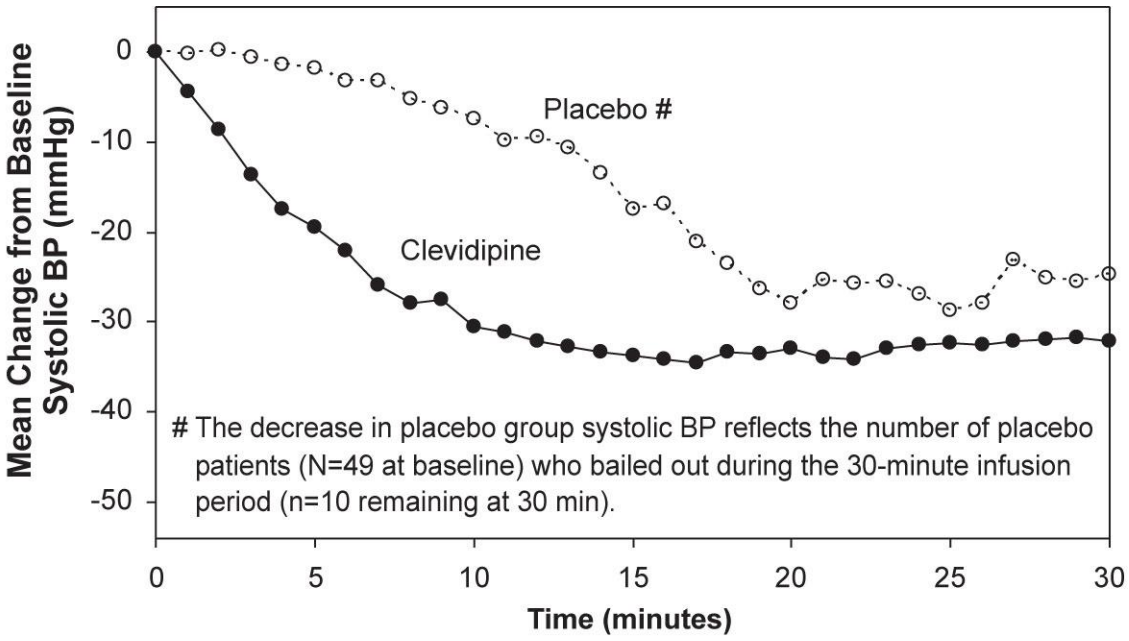


Figure 2. Mean change in systolic blood pressure (mmHg) during 30-minute infusion, ESCAPE-2 (postoperative)



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

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

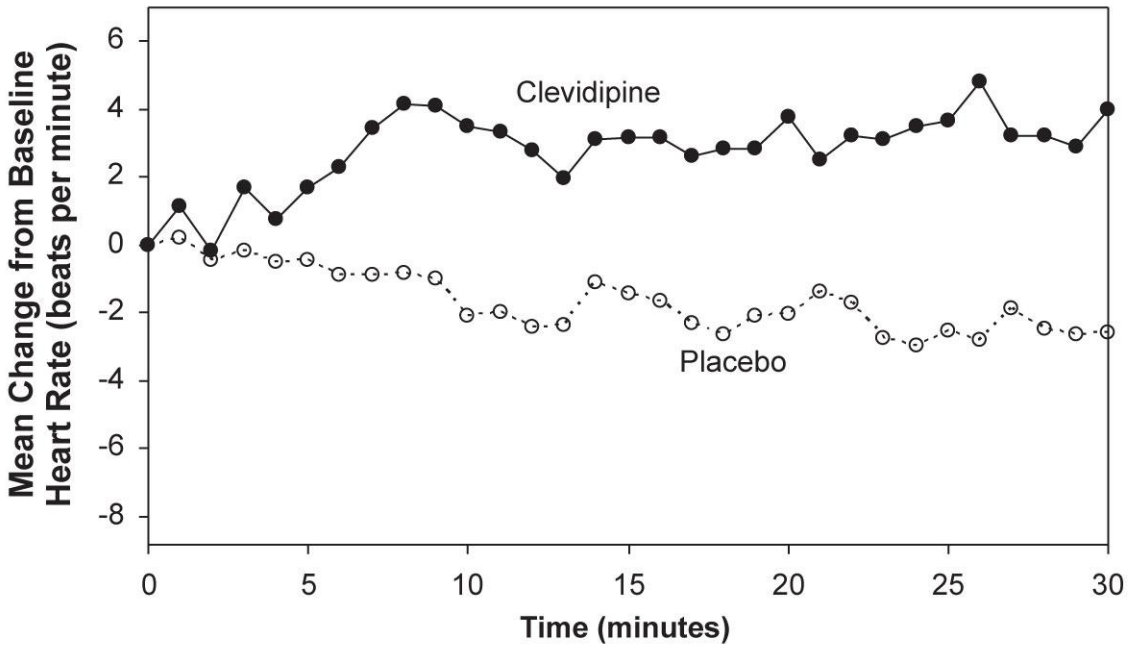
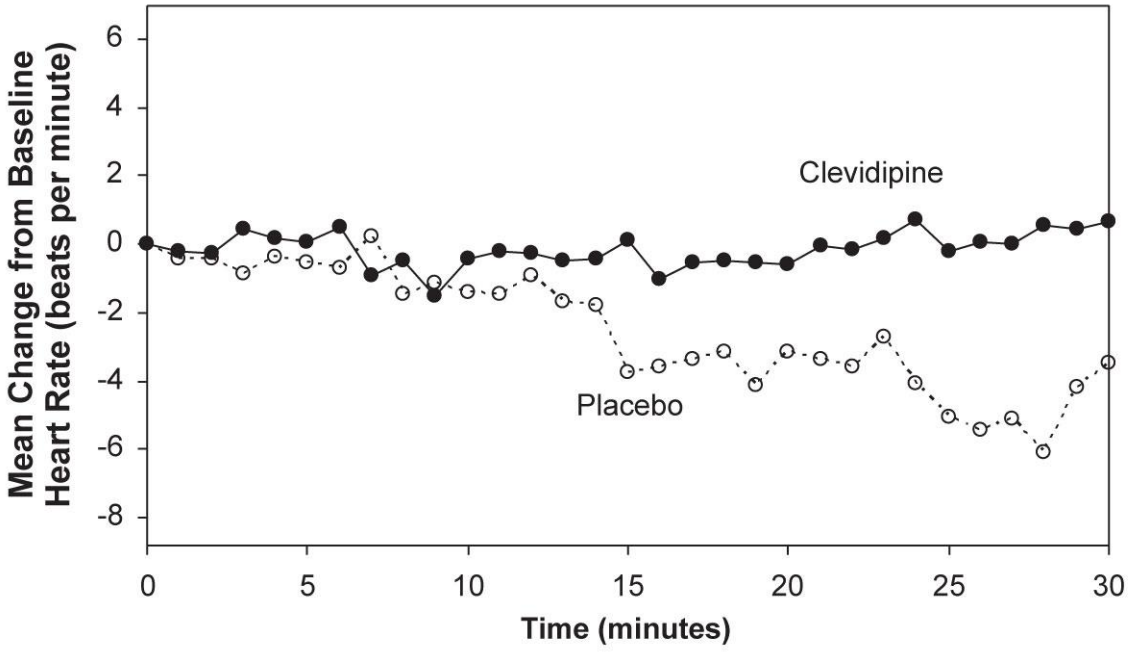


Figure 4. Mean change in heart rate (bpm) during 30-minute infusion, ESCAPE-2 (postoperative)



In three Phase 3, actively controlled, open-label clinical trials (ECLIPSE), 1,506 patients were randomised and received Cleviprex (n=752), nitroglycerine (NTG; perioperative, n=278), sodium nitroprusside (SNP; perioperative, n=283), or nicardipine (NIC; postoperative, n=193; not registered in Australia) for the treatment of hypertension in cardiac surgery. The mean exposure in the ECLIPSE studies was 8 hours at 4.5 mg/hour for the 752 patients who were treated with Cleviprex. Blood pressure control was assessed by measuring the magnitude and duration of SBP excursions outside the predefined pre- and post-operative SBP target range of 75-145 mmHg and the predefined intra-operative SBP range of 65-135 mmHg. In general, blood pressure control was similar across the four treatment groups. The primary safety endpoint was a comparison of the clinical events of death, myocardial infarction (MI), stroke, and renal dysfunction at 30 days post-surgery. Data regarding the primary safety endpoint are presented in the Adverse Effects section, Table 2.

Essential Hypertension

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

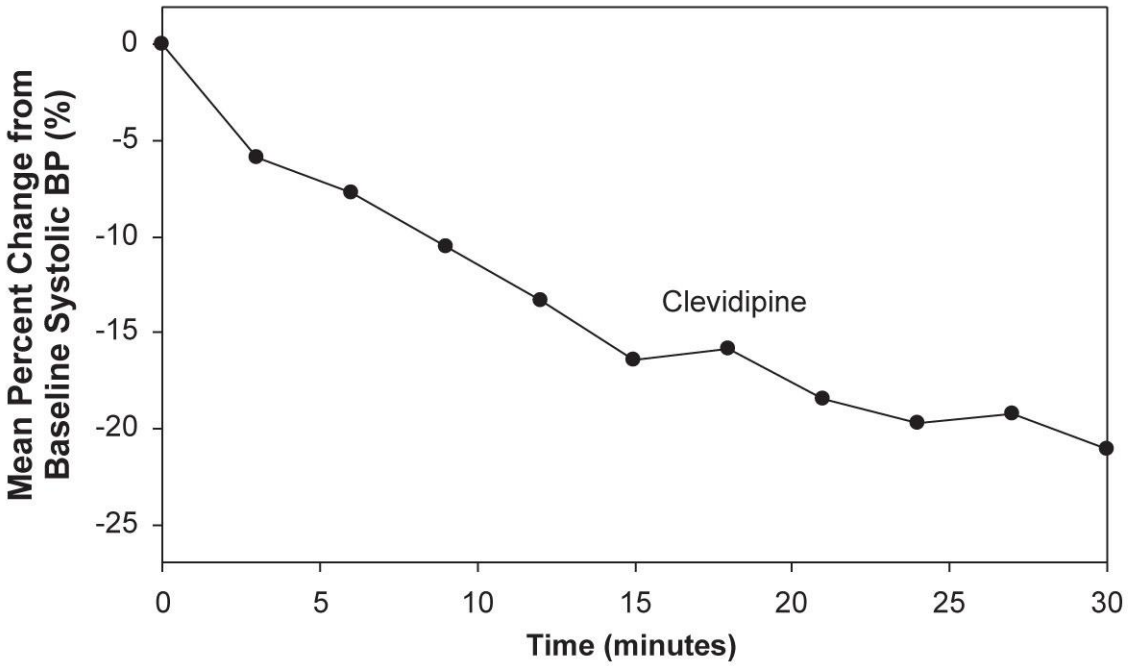
Subjects were randomized to placebo or to 2, 4, 8, or 16 mg/hour. Doses above 2 mg/hour were started at 2 mg/hour and force-titrated in 2-fold increments at 3-minute intervals. Blood pressure, heart rate, and blood levels of clevidipine were measured during the infusion period. Blood levels were monitored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

Severe Hypertension

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

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

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



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

5.2 PHARMACOKINETIC PROPERTIES

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

ABSORPTION

Clevidipine is >99.5% bound to proteins in plasma at 37°C.

DISTRIBUTION

The steady state volume of distribution was determined to be 0.17 L/kg in arterial blood.

METABOLISM

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

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

EXCRETION

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

5.3 PRECLINICAL SAFETY DATA

GENOTOXICITY

Clevidipine displayed positive genotoxic potential in in vitro assays (Ames test, mouse lymphoma thymidine kinase locus assay, chromosomal aberration assay) but not in vivo in the mouse micronucleus test. The positive in vitro results are consistent with the formation of formaldehyde, a minor metabolite of clevidipine, which is known to be genotoxic in vitro and a probable human carcinogen. However, human in vivo exposure to formaldehyde at the maximum clinical dose of clevidipine (32 mg/h) is at least several hundred times less than normal daily endogenous formaldehyde generation, and is therefore not of clinical concern.

CARCINOGENICITY

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Soya oil, glycerol, egg lecithin, oleic acid, disodium edetate, water for injection and sodium hydroxide to adjust pH.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2-8°C. Do not freeze. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Cleviprex is supplied in sterile, single-use, pre-mixed 25mg/50 mL and 50mg/100 mL glass vials.

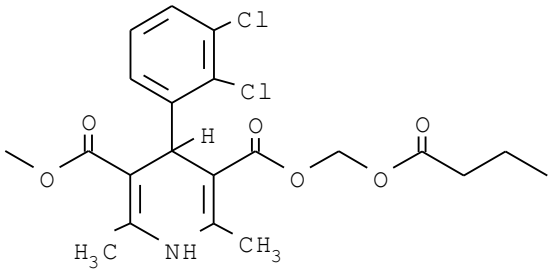
Cleviprex is supplied in single vials inside a carton. Each pack includes 10 cartons containing single-use vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CHEMICAL STRUCTURE



CAS NUMBER: 167221-71-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Emerge Health Pty Ltd
Suite 3, 22 Gillman Street
Hawthorn East, VIC. 3123
AUSTRALIA

9. DATE OF FIRST APPROVAL

9 APRIL 2010

10. DATE OF REVISION

25 JANUARY 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Updated formatting of PI to match new format approved by the TGA 8 Novemeber 2017
Section 8	Updated Sponsor address following office rellocation