

Data Sheet

CLEVIPREX™

Clevidipine butyrate 25 mg/ 50mL and 50 mg/100 mL injectable emulsion vials

Presentation

Cleviprex™ is a sterile, milky-white opaque emulsion in a vial containing 0.5 mg/mL of clevidipine butyrate for intravenous use.

Uses

Actions

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

Pharmacodynamic effects

Cleviprex™ is titrated to achieve the desired reduction in blood pressure. The dose may be doubled every 90 seconds and should be continued until the target blood pressure is reached. 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 WARNINGS AND PRECAUTIONS)

The effect of Cleviprex™ in anaesthetised cardiac surgery patients on central haemodynamics, myocardial blood flow and metabolism were studied. In these patients, cardiac output and stroke volume increased by 10%. As the dose of Cleviprex™ was

escalated, myocardial oxygen extraction decreased significantly, indicating preservation of myocardial perfusion and a direct coronary vasodilatory effect. No increase in net lactate production in coronary sinus blood was observed, confirming the absence of myocardial ischaemia due to coronary steal.

Pharmacokinetics

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

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

Metabolism and Elimination: Clevidipine butyrate is rapidly metabolised by hydrolysis of the ester linkage, primarily by esterases in the blood and extravascular tissues, making its elimination unlikely to be affected by hepatic or renal dysfunction. The primary metabolite is the carboxylic acid metabolite 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 show that clevidipine butyrate and its metabolite will not inhibit or induce any CYP enzyme at the concentrations achieved in clinical practice.

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

Indications

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

Dosage and Administration

Adults/Elderly

Cleviprex™ is intended for intravenous use. 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.

Initial dose: Initiate the intravenous infusion of Cleviprex™ at 2 mg/h; the dose may be doubled every 90 seconds. 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.

Maximum dose: In clinical studies most patients were treated with maximum doses of 16 mg/h or less. There is limited clinical experience in doses over 32 mg/h. No more than 1000 mL of Cleviprex™ infusion is recommended in the initial 24-hour period due to the associated potential lipid load. There is little experience with infusion durations beyond 72 hours at any dose.

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

Special populations

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

Paediatric population

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

Patients on other lipid-based therapies

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

Instructions for Use/Handling

Refer PHARMACEUTICAL PRECAUTIONS SECTION.

Contraindications

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

Warnings and Precautions

Use strict aseptic technique and discard any unused product within 12 hours of stopper puncture.

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.

Hypotension and reflex tachycardia

Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia. If either occurs with Cleviprex™, decrease the dose.

Critical aortic stenosis

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

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 – 6mg/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.

Pregnancy and Lactation

Use in Pregnancy – Category C

There are no adequate data from the use of Cleviprex™ in pregnant women.

Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown.

Cleviprex™ should not be used during pregnancy unless clearly necessary.

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.

Paediatric Use

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

Use in the elderly

Of the 1406 subjects (1307 with hypertension) treated with Cleviprex™ in clinical studies, 620 were ≥ 65 years of age and 232 were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these and younger patients and no dose adjustment is required.

Carcinogenicity

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

Genotoxicity

Cleviprex™ displayed positive genotoxic potential in *in vitro* assays. Formaldehyde, a minor metabolite of clevidipine butyrate, appears to be responsible for the positive *in vitro* results. Formaldehyde exposures from maximum clinical doses (32 mg/h) of clevidipine are 278 fold below documented endogenous human exposures and are not considered a safety risk to humans. Long-term studies for evaluation of carcinogenic potential have not been performed with clevidipine butyrate due to the intended short-term duration of human use.

Adverse Effects

Cleviprex™ has been evaluated for safety in 1,307 hypertensive patients, among whom 5% were treated with the mean dose of >16 mg/h and up to the maximum recommended therapeutic dose of 32 mg/h, and 25% were continuously infused for more than 15 hours and up to 72 hours. The incidence of adverse reactions showed no association with gender, age, race or ethnicity.

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%, 12.0%, and 32.9%, 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 adverse reactions (Table 1: Perioperative hypertension; Table 2: Essential hypertension; Table 3: Severe 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: common = $\geq 1\%$; uncommon $< 1\%$ but $\geq 0.1\%$ and rare = $< 0.1\%$. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 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 2 Adverse drug reactions in essential hypertension patients

Nervous system disorders	
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

Table 3 Adverse drug reactions in severe hypertension patients

Gastrointestinal disorders	
Common:	Nausea

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

Interactions

Pharmacokinetic drug interactions are unlikely as clevidipine is metabolised by hydrolysis *in vivo*. No formal drug-drug interaction studies were conducted.

Clevidipine butyrate and its major dihydropyridine metabolite do not have the potential for inhibiting or inducing any CYP enzyme.

Overdosage

The maximum recommended dose is 32 mg/h. In clinical trials, 1 healthy subject received a dose of Cleviprex™ up to 106 mg/h and experienced mild flushing and a slight transient increase in serum creatinine.

As a result of a weight-based regimen, 49 patients received a maximum rate above 32 mg/h without any clinical difference in the incidences of adverse events compared to those who received 32 mg/h or below. The average dose in these patients was 41 mg/h with a maximum dose of 60 mg/h.

One cardiac surgical patient received a bolus dose of Cleviprex™ prior to aortic cannulation and experienced hypotension.

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.

Pharmaceutical Precautions

Store at 2 - 8°C. Do not freeze. Protect from light. Vials in cartons may be transferred to controlled room temperature for a period not to exceed 2 months. Do not return to refrigerated storage after beginning room temperature storage. Cleviprex™ has a shelf life of 36 months (3 years).

Instructions for Use/Handling

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 microorganisms. Do not use if contamination is suspected. Once the stopper is punctured, use within 12 hours and discard any unused portion.

Cleviprex™ is a sterile, milky-white opaque emulsion. Visually inspect for particulate matter and discoloration 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.

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Cleviprex is compatible when co-infused with: Water for Injection, Sodium Chloride (0.9%) Solution for Injection, Dextrose (5%) Solution for Injection, Dextrose (5%) in Sodium Chloride (0.9%) Solution for Injection, Dextrose (5%) in Ringer's Lactate Solution for Injection, Lactated Ringer's Solution for Injection, 10% amino acid.

Medicine Classification

Prescription Medicine.

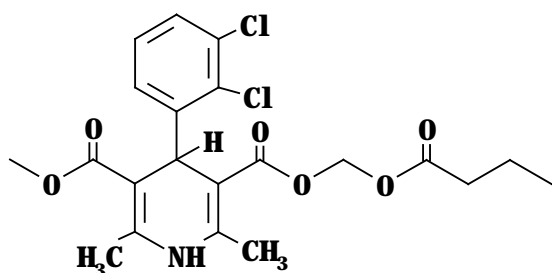
Package Quantities

Cleviprex™ 25mg in 50mL vials, Pack of 10 vials
Cleviprex 50mg in 100mL vials, Pack of 10 vials

Further Information

Description

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



CAS number: 167221-71-8

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

Molecular formula: C₂₁H₂₃Cl₂NO₆.

MW: 456.3

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

List of Excipients

In addition to the active ingredient clevidipine butyrate, Cleviprex™ also contains soybean oil, glycerine, purified egg yolk phospholipids and sodium hydroxide (pH adjustment)

Cleviprex™ has a pH of 6.0 – 8.8 and is a ready-to-use emulsion.

Clinical Trials

Perioperative patients

Cleviprex™ was evaluated in two Phase 3 double-blind, randomised, placebo-controlled trials of 105 and 110 cardiac surgery patients (ESCAPE-1, preoperative, and ESCAPE-2, postoperative, respectively) with perioperative hypertension (SBP ≥160 mmHg). The primary endpoint was bailout defined by premature and permanent discontinuation of study drug, with patients transferred to alternative open-label therapy.

In greater than 90% of patients treated with Cleviprex™, blood pressure was lowered by ≥15% within 30 minutes. Bailout rates in ESCAPE-1 were 7.5% Cleviprex™ vs. 82.7% placebo. Similarly ESCAPE-2 had bailout rates of 8.2% Cleviprex™ vs. 79.6% for placebo.

Blood-pressure-lowering effect with Cleviprex™ was seen within 2 minutes. The median time to attain the target SBP was 6 minutes and 5.3 minutes for ESCAPE-1 and ESCAPE-2, respectively.

There were no treatment-emergent adverse reactions in the ESCAPE-1 trial. Treatment-emergent adverse reactions for ESCAPE-2 were atrial fibrillation (Cleviprex™ – 1.6%; placebo – 0%), and insomnia (Cleviprex™ – 1.6%; placebo – 0.0%).

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). 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. The primary efficacy endpoint was blood pressure control defined as the area under the curve (AUC) capturing the magnitude and duration of blood pressure excursions outside of a predefined range.

Data regarding the primary safety endpoint is presented in Table 4

Table 4. Primary endpoint data for the ECLIPSE trials

	Clevipidine (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%)

Regarding efficacy, Cleviprex™ provided better blood pressure control compared to NTG (AUC_{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 Cleviprex™ and NIC was similar (median 1.76 vs. 1.69 mmHg x min/h, respectively, p=0.8508) in the postoperative setting.

The adverse events observed during the treatment infusion period up to 1 hour after the end of the infusion were similar in patients who received Cleviprex™ and in those who received comparator agents. 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.

Essential hypertension

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

Subjects were randomised to placebo or to 2, 4, 8, or 16 mg/h. All patients initiated therapy at 2 mg/h and force-titrated in 2-fold increments at 3-minute intervals. Blood pressure and heart rate were measured during the infusion period and for 8 and 96 hours post-infusion.

Cleviprex™ blood concentrations were monitored during and for 1 hour post-infusion.

Systolic blood pressure effect was related to the concentration of Cleviprex™ and plateaued at higher measured concentrations. The estimated infusion rate necessary to achieve half of this maximal effect was approximately 10 mg/h. There was no incidence of rebound hypertension following discontinuation of infusion.

Severe hypertension patients

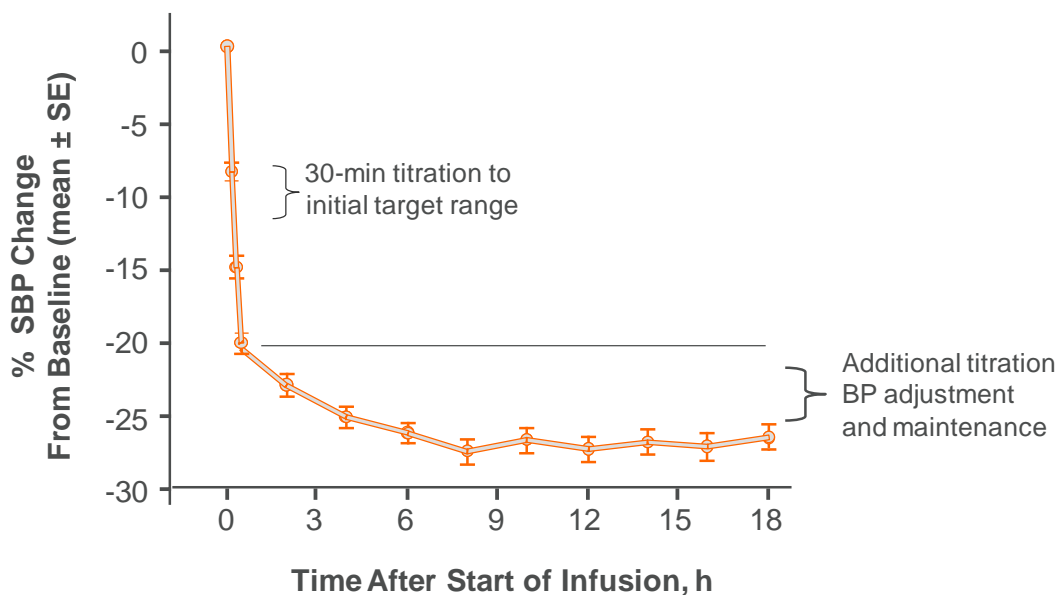
Cleviprex™ was evaluated in an open-label Phase 3 clinical trial (VELOCITY) in 126 patients with severe hypertension (SBP >180 mmHg or diastolic blood pressure [DBP] >115 mmHg) of which 81% (102/126) of patients had hypertension-related end-organ injury.

Cleviprex™ rapidly and predictably lowered blood pressure to an individualised, prespecified target in 89% of patients with a mean decrease of 21.1% at 30 minutes. The median time to achieve target SBP range was 10.9 minutes, at a median dose of 8 mg/h.

Following achievement of the initial target, the majority of patients (92.3%) were managed without the use of additional IV antihypertensive agents during the ≥18 hour infusion period with minimal change to the infusion rate.

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

Figure 1. Mean percentage change in SBP from baseline during 18 hours of clevidipine infusion



In the ESCAPE, ECLIPSE and VELOCITY studies there were no significant differences in efficacy and safety across subgroups of patients defined by gender, age or race.

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