

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrCLEVIPREX™**

Clevidipine Injection

Emulsion for infusion 0.5 mg/mL for intravenous use

Dihydropyridine derivative

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

CLEVIPREX (clevidipine) is indicated for:

- The management of acute elevation of blood pressure in perioperative settings.

#### **1.1 Pediatrics (<18 years of age):**

The safety and effectiveness of CLEVIPREX in children under 18 years of age have not been established.

#### **1.2 Geriatrics (≥65 years of age):**

Of the 1406 subjects treated with CLEVIPREX during clinical studies (1307 with hypertension), 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. No dosage adjustment is required.

### **2 CONTRAINDICATIONS**

CLEVIPREX is contraindicated in patients with:

- Allergy to clevidipine, soybeans, soybean oil, soy products, eggs or egg products, or peanut.
- Defective lipid metabolism such as pathologic hyperlipidemia, lipid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia.
- Severe aortic stenosis (see [7 WARNINGS AND PRECAUTIONS](#)).

### **4 DOSAGE AND ADMINISTRATION**

#### **4.1 Dosing Considerations**

- Blood pressure and heart rate should be monitored continuously during infusion and afterwards until vital signs are stable. Patients who are on prolonged infusions should be monitored for the possibility of rebound hypertension for at least 8 hours after stopping the infusion.

#### **4.2 Recommended Dose and Dosage Adjustment**

CLEVIPREX is intended for intravenous use only. Titrate the drug to achieve the desired blood pressure reduction. Individualize dosage depending on the blood pressure to be obtained and the response of the patient.

Initial dose: Initiate the intravenous infusion of CLEVIPREX at a rate of 1 to 2 mg/h.

Dose titration: The dose may be doubled at short (90 second) intervals until the desired blood pressure level is about to be reached. Continue titration until the desired target range is achieved by increasing the dose in smaller increments and at longer intervals (5 to 10 minutes). A 1 to 2 mg/h increase will generally produce an additional 2 to 4 mmHg decrease in systolic pressure.

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

Maximum dose: The maximum dose is 32 mg/h, although most patients were treated with doses of 16 mg/h or less. 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 anti-hypertensive agent: Discontinue CLEVIPREX or titrate downward while appropriate oral therapy is established. When an oral anti-hypertensive 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.

Hepatic or Renal Impairment: During clinical trials, there was limited experience in patients with hepatic or renal impairment. From all clinical trials, there were 78 patients with abnormal liver function and 121 patients with moderate to severe renal impairment. No dose adjustment was required for these patients.

Health Canada has not authorized an indication for pediatric use.

Table 1 provides a guideline for dosing conversion from mg/h to mL/h.

**Table 1 CLEVIPREX Dosing Conversion from mg/h to mL/h**

Dose (mg/h)	Dose (mL/h)
1	2
2	4
4	8
6	12
8	16
10	20
12	24
14	28
16	32
18	36
20	40
22	44
24	48
26	52
28	56
30	60
32	64

#### 4.4 Administration

Maintain strict aseptic technique while handling CLEVIPREX. CLEVIPREX is a single-use parenteral

product that contains 0.005% disodium edetate to inhibit the rate of growth of microorganisms, for up to 12 hours, in the event of accidental contamination. However, CLEVIPREX can still support the growth of microorganisms, as it is not an antimicrobially preserved product under USP standards. Do not use if contamination is suspected. Once the stopper is punctured use within 12 hours and discard any unused portion (see [7 WARNINGS AND PRECAUTIONS](#)).

CLEVIPREX is supplied in sterile, single-use, pre-mixed, ready-to-use 50 mL or 100 mL vials. Invert vial gently several times before use to ensure uniformity of the emulsion prior to administration. Inspect parenteral drug products for particulate matter and discoloration prior to administration. Discard products that are discoloured or contain particulate matter. Administer CLEVIPREX using an infusion device allowing calibrated infusion rates. Commercially available standard plastic cannulae may be used to administer the infusion. Administer CLEVIPREX by either a central line or peripheral line.

Lipid filters with a 1.2 micron pore size may be used when administering CLEVIPREX.

CLEVIPREX should not be infused in the same line as other medications.

CLEVIPREX should not be diluted, but it can be administered with any of the following:

- Water for Injection, USP
- Sodium Chloride (0.9%) Injection, USP
- Sodium Chloride (0.45%) Injection
- Dextrose (5%) Injection, USP
- Dextrose (5%) in Sodium Chloride (0.9%) Injection, USP
- Dextrose (5%) in Ringers Lactate Injection, USP
- Lactated Ringers Injection, USP
- 40 meq Potassium Chloride in 0.9% Sodium Chloride
- 10% amino acid

## 5 OVERDOSAGE

There has been no experience of overdose in human clinical trials.

In clinical trials 1 healthy subject was titrated to a dose above the normal recommended limit (up to 106 mg/h) and experienced mild flushing and a slight transient increase in serum creatinine.

The expected major effects of overdose would be hypotension and reflex tachycardia.

When CLEVIPREX is discontinued, blood pressure returns to baseline pre-treatment levels within 5 to 15 minutes (see [10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics](#)). In a case of suspected overdose, CLEVIPREX should be discontinued immediately and the patient's blood pressure should be supported and monitored.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 2 Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Emulsion for infusion, for	Edetate disodium, glycerin, oleic acid, purified

	intravenous use 0.5 mg/mL clevidipine	egg yolk phospholipids, sodium hydroxide (for pH adjustment), soybean oil, water for injections
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CLEVIPREX (clevidipine) Emulsion for Intravenous Infusion 0.5 mg/mL is supplied as a sterile, milky-white oil-in-water emulsion for intravenous injection.

Available as:

- 50 mL single use glass vial containing 0.5 mg/mL clevidipine.
  - Each vial is individually packaged in its own carton.
  - Available in boxes of 10 vials.
- 100 mL single use glass vial containing 0.5 mg/mL clevidipine.
  - Each vial is individually packaged in its own carton.
  - Available in boxes of 10 vials.

Vials are sealed with 32 mm grey bromobutyl rubber stoppers and capped with 32 mm “Flip-Off” aluminum overseals, which keep the stopper in its proper position in the neck of the vial.

## 7 WARNINGS AND PRECAUTIONS

### General

CLEVIPREX is a single-use parenteral product that contains phospholipids and can support microbial growth. Strict aseptic technique must be adopted while handling CLEVIPREX. Once the stopper is punctured, use within 12 hours and discard any unused portion.

CLEVIPREX should not be administered in the same line with other medications and should not be diluted (see [4 DOSAGE AND ADMINISTRATION](#)).

### Cardiovascular

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

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

CLEVIPREX is contraindicated in patients with critical aortic stenosis because excessive afterload reduction can reduce myocardial oxygen delivery in these patients.

There was no evidence of significant rebound hypertension following discontinuation of CLEVIPREX infusion. Patients who receive prolonged or high doses of CLEVIPREX should be monitored for at least 8 hours.

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

### Endocrine and Metabolism

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

*Patients on other lipid-based therapy*

CLEVIPREX contains approximately 0.2 g of lipid per millilitre (8.4 kJ/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 clevidipine formulation.

### **Hepatic/Biliary/Pancreatic**

Patients with underlying hepatic, biliary, or pancreatic conditions were not specifically studied. Clinical trials included 78 patients with elevated serum bilirubin, AST/SGOT, and/or ALT/SGPT. Because clevidipine is rapidly metabolized in the blood and extravascular tissues, its elimination is unlikely to be affected by hepatic dysfunction and dosage adjustments are therefore not required (see [10.3 Pharmacokinetics](#)).

### **Monitoring and Laboratory Tests**

Blood pressure and heart rate should be monitored continuously during and after the infusion until vital signs are stable (see [7 WARNINGS AND PRECAUTIONS](#) and [4 DOSAGE AND ADMINISTRATION](#)).

### **Renal**

Patients with underlying renal conditions were not specifically studied. In clinical trials, 121 patients with moderate to severe renal impairment were treated with CLEVIPREX. No clinically important differences or safety signals were observed. As clevidipine elimination is unlikely to be affected by renal dysfunction, dosage adjustments are not required (see [10.3 Pharmacokinetics](#)).

### **Reproductive Health: Female and Male Potential**

- **Fertility**

There were no adverse effects on fertility or mating behaviour of male rats with clevidipine doses of up to 55 mg/kg/day. Female rats demonstrated pseudopregnancy and changes in estrus cycle at doses as low as 13 mg/kg/day; however, doses of up to 55 mg/kg/day did not affect mating or fertility (see [16 NON-CLINICAL TOXICOLOGY](#)).

When pregnant rats were dosed with clevidipine during late gestation and early lactation (terminating on day 4 post-partum), there were dose-related increases in mortality, length of gestation, and prolonged parturition at dose levels as low as 13 mg/kg/day. When offspring of these dams were mated, they had a conception rate lower than that of controls. Clevidipine crosses the placental membrane in this species and doses of  $\geq 35$  mg/kg/day administered during organogenesis adversely affected fetal survival. Fetal survival was also adversely affected when pregnant rabbits were treated during organogenesis with 55 mg/kg/day (see [16 NON-CLINICAL TOXICOLOGY](#)).

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

There have been no studies of CLEVIPREX use in pregnant women. CLEVIPREX should only be used during pregnancy if the potential benefit to the mother outweighs the potential risk to the fetus (see [16 NON-CLINICAL TOXICOLOGY](#)).

The safety and efficacy of CLEVIPREX during labour and delivery have not been established. Other calcium channel blockers are known to suppress uterine contractions in humans. Pregnant rats treated with clevidipine during late gestation showed an increased rate of prolonged parturition (see [16 NON-CLINICAL TOXICOLOGY](#)).



### 7.1.2 Breast-feeding

It is not known if clevidipine is excreted in human milk. Because many drugs are excreted in human milk, consider possible infant exposure when CLEVIPREX is administered to a nursing mother.

### 7.1.3 Pediatrics

**Pediatrics (<18 years):** The safety and effectiveness of CLEVIPREX in children under 18 years of age have not been established.

### 7.1.4 Geriatrics

In limited experience with CLEVIPREX in elderly patients, no differences were identified in the clinical response of patients over 65 years of age and younger patients.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

CLEVIPREX (clevidipine) was administered to 1099 hypertensive patients in peri-operative settings. No association between gender, age, race, or ethnicity and the incidence of adverse events was observed.

Although infusions of lipid containing products may be associated with increases in triglycerides, no consistent changes in triglyceride levels were observed with CLEVIPREX.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

There were many adverse events associated with the operative procedure, but relatively few that could plausibly be related to the anti-hypertensive drugs. Thus, the ability to differentiate the adverse event profile between treatments was limited. The incidence of adverse events leading to the discontinuation of the study drug was 5.9% of patients receiving CLEVIPREX and 3.2% for all active comparators. The most common adverse reactions leading to study drug discontinuation in all groups were hypertension and, when combined with a beta-blocker, hypotension. The incidence of serious adverse events and associated discontinuation rates within 1 hour of the drug infusion were similar among patients receiving CLEVIPREX and all active comparators.

#### Placebo-controlled peri-operative studies

The placebo-controlled experience with CLEVIPREX in the peri-operative setting was both small and brief (about 30 minutes).

[Table 3](#) lists the treatment-emergent adverse events and the category “any common adverse event” in the ESCAPE-1 and ESCAPE-2 studies (see [14 CLINICAL TRIALS](#)).

**Table 3 Common Adverse Events in Placebo-controlled Peri-operative Studies**

Adverse Event	ESCAPE-1		ESCAPE-2	
	CLEVIPREX N=53 n (%)	Placebo N=51 n (%)	CLEVIPREX N=61 n (%)	Placebo N=49 n (%)
Any common <sup>1</sup> adverse event	27 (51%)	21 (41%)	32 (53%)	24 (49%)
<b>Cardiac disorders</b>				
Atrial fibrillation	7 (13%)	6 (12%)	13 (21%)	6 (12%)
<b>Gastrointestinal disorders</b>				
Nausea	3 (6%)	5 (10%)	13 (21%)	6 (12%)
<b>General disorders and administration site conditions</b>				
Pyrexia	11 (19%)	7 (14%)	3 (5%)	3 (6%)
<b>Psychiatric disorders</b>				
Insomnia	NR <sup>2</sup>	NR <sup>2</sup>	7 (12%)	3 (6%)
<b>Renal and urinary disorders</b>				
Acute renal failure	5 (9%)	1 (2%)	4 (7%)	4 (8%)
<b>Respiratory, thoracic and mediastinal disorders</b>				
Atelectasis	3 (6%)	0 (0%)	NR <sup>2</sup>	NR <sup>2</sup>

<sup>1</sup> Where the rate with CLEVIPREX exceeded the rate with placebo by at least 5% in one of the two trials.

<sup>2</sup> Not reported.

### Peri-operative clinical studies using active controls

Three studies called ECLIPSE compared CLEVIPREX to three active controls: nitroglycerin, sodium nitroprusside, and nicardipine (see [14 CLINICAL TRIALS](#)). Drug exposure in these studies was longer, the pooled mean maximum dose being 10 mg/h, and the mean duration of treatment was 8 hours. The adverse events observed within 1 hour of the end of the infusion were similar in all patients who received CLEVIPREX and those who received the comparator drugs.

Rebound hypertension was assessed as the maximum increase in systolic blood pressure (SBP) from the last measurement on study drug to 1 hour after termination of the study drug. In both the CLEVIPREX and active comparator groups, 10.7 to 12% of patients exhibited greater than 30% increase in SBP.

#### 8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety and effectiveness of CLEVIPREX in children under 18 years of age have not been established.

#### 8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions occurring in patients treated with CLEVIPREX at a higher frequency than placebo in the ESCAPE-1 or ESCAPE-2 trials included:

**Blood and lymphatic system disorders:** anemia, coagulopathy, leukocytosis

**Cardiac disorders:** right bundle branch block, pericarditis, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, tachycardia, ventricular bigeminy, ventricular extrasystoles, ventricular tachycardia

**Gastrointestinal disorders:** bowel sounds abnormal, constipation, diarrhea

**General disorders and administration site conditions:** anasarca, application site reaction, asthenia, chest discomfort, chest pain, peripheral edema, induration, nodule, secretion discharge

**Infections and infestations:** bacteremia, bacterial infection, bronchitis, cellulitis, oral candidiasis, pneumonia, urinary tract infection, wound infection

**Injury, poisoning and procedural complications:** postoperative anemia, incision site complication, medical device complication, postoperative ileus, post procedural hemorrhage

**Investigations:** abnormal blood gases, decreased cardiac output, abnormal QRS complex electrocardiogram, Gram stain positive, increased international normalised ratio, abnormal liver function test, increased troponin

**Metabolism and nutrition disorders:** acidosis, diabetes mellitus, hyperglycemia, hyponatremia, malnutrition, metabolic acidosis

**Musculoskeletal and connective tissue disorders:** back pain, muscle spasms

**Nervous system disorders:** cerebrovascular accident, dizziness, headache

**Psychiatric disorders:** abnormal behaviour, agitation, anxiety, confusional state, delirium, depression, disorientation, restlessness

**Renal and urinary disorders:** incontinence, oliguria, nephrolithiasis, renal insufficiency

**Respiratory, thoracic and mediastinal disorders:** acute respiratory distress syndrome, cough, diaphragmatic paralysis, dyspnea, hypoxia, mediastinal hemorrhage, nasal congestion, pleural effusion, pulmonary edema, respiratory distress, respiratory failure, throat tightness, wheezing

**Skin and subcutaneous tissue disorders:** decubitus ulcer, hyperhidrosis, subcutaneous emphysema

**Surgical and medical procedures:** nasal sinus drainage

**Vascular disorders:** hemorrhage, hypertension, hypotension, thrombophlebitis

### 8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

The safety and effectiveness of CLEVIPREX in children under 18 years of age have not been established.

## 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

### Clinical Trial Findings

Laboratory analyses were performed as part of all clinical studies. Individual hematologic and clinical chemistry abnormalities occurred in <0.5% of all patients.

## 8.5 Post-Market Adverse Reactions

CLEVIPREX was first marketed in September 2008 (US). Adverse events reported globally since market introduction include: tachycardia, respiratory gas exchange disorder (ventilation perfusion mismatch and oxygen saturation decrease), ileus, hypersensitivity, and infusion site reaction. Post-marketing data are often insufficient to support an estimate of incidence or to firmly establish causation.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

No formal clinical interaction studies were conducted. Pharmacokinetic drug interactions are unlikely to occur as clevidipine is metabolized by hydrolysis. Clevidipine and its major dihydropyridine metabolite do not have the potential for blocking or inducing any CYP enzymes when used in the therapeutic dose range.

### 9.3 Drug-Behavioural Interactions

Interactions with behavioural risks have not been established.

### 9.4 Drug-Drug Interactions

During clinical trials, 801 of 866 peri-operative patients treated with CLEVIPREX received some type of beta-blocker. Other frequently used concomitant medications in these patients included natural opium alkaloids, benzodiazepine derivatives, and sulfonamides. In patients with severe hypertension, the most frequently used classes of concomitant medications were imidazoline receptor agents, angiotensin converting enzyme (ACE) inhibitors, and selective beta-blocking agents. There was no pattern of increased adverse events in the presence of these concomitant medications (see [8 ADVERSE REACTIONS](#) and [10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics](#)).

In the Phase III peri-operative studies, patients receiving a concomitant beta-blocker during the CLEVIPREX infusion experienced a similar incidence of hypotension or labile blood pressure (12.3%) as did those not receiving a beta-blocker (15.4%). Only one patient with severe hypertension (2.2%) experienced hypotension while receiving a concomitant beta-blocker.

Interactions with other drugs have not been established.

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

CLEVIPREX contains the active ingredient clevidipine, a 1,4-dihydropyridine L-type calcium channel antagonist. It lowers arterial blood pressure by decreasing systemic vascular resistance due to an action mainly on resistance (arterial) blood vessels.

Experiments in anesthetized rats and dogs showed 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.

#### In vitro

Whole cell patch clamp experiments using rabbit isolated ventricular cells demonstrated that the primary mechanism of action of clevidipine is the inhibition of the calcium current in L-type calcium channels. In isolated organ bath experiments, clevidipine reduced the contraction of portal vein smooth muscle and heart papillary muscle in a concentration-dependent manner, but this action was of greater potency on vascular tissue with a selectivity ratio of about 50.

### In vivo

Clevidipine had dose-dependent hypotensive effects in rats and dogs. In conscious but not in anesthetized animals, the heart rate was also increased by clevidipine in a dose-dependent manner. In anesthetized spontaneously hypertensive rats (SHR), the two enantiomers of clevidipine had similar hypotensive potency and duration of effect as did the racemic clevidipine. Formulated clevidipine was found to be more potent than nitroglycerin. The potency of sodium nitroprusside was similar to nicardipine and was less potent than felodipine and isradipine. Moreover, clevidipine was shorter acting than the latter three drugs, and was similarly and slightly longer acting than nitroglycerin and sodium nitroprusside, respectively.

In anesthetized beagle dogs, clevidipine caused a relaxation of vascular smooth muscle, which resulted in a 40% reduction in total peripheral resistance at the highest dose level of 24.84 ug/kg/min and caused increased cardiac output because of increased stroke volume. Clevidipine did not, however, have negative inotropic, chronotropic, or dromotropic effects and did not induce venous dilation in anesthetized dogs. These results confirmed *in vitro* findings that clevidipine has high vascular versus myocardial selectivity and also showed a high arterial versus venous selectivity.

## **10.2 Pharmacodynamics**

CLEVIPREX has a rapid onset and offset activity which allows titration of arterial pressure. The effect of CLEVIPREX appears to plateau at approximately 25% of baseline systolic pressure. The infusion rate for which half the maximal effect is observed is approximately 10 mg/h.

Onset of Effect: In the peri-operative patient population, CLEVIPREX produced a 4% to 5% reduction in systolic blood pressure within 2 to 4 minutes after starting a 0.4 ug/kg/min infusion (approximately 2 mg/h).

Maintenance of Effect: In studies up to 72 hours of continuous infusion, there was no evidence of tachyphylaxis or hysteresis.

Offset of Effect: Most patients returned to pre-treatment baseline values in 5 to 15 minutes after the infusion was stopped.

Hemodynamics: CLEVIPREX causes a dose-dependent decrease in systemic vascular resistance. It exerts a favourable effect on cardiac hemodynamic parameters due to its arterial-selective effect, resulting in decreased systemic vascular resistance without changes in venous tone.

Heart Rate: A reflex-induced increase in heart rate is an expected response to a decrease in blood pressure. In some patients the increase in heart rate may be pronounced (see [7 WARNINGS AND PRECAUTIONS](#)).

Electrophysiologic Effects: In healthy volunteers, neither clevidipine nor its major carboxylic acid metabolite prolonged cardiac repolarization at therapeutic and supratherapeutic concentrations.

### 10.3 Pharmacokinetics

**Table 4 Summary of Clevidipine Pharmacokinetic Parameters in Healthy Population and Perioperative Hypertension**

	<b>t<sub>½</sub> (initial phase) (min)</b>	<b>t<sub>1/2</sub> (terminal phase) (min)</b>	<b>CL (L/min/kg)</b>	<b>Vd (L/kg)</b>
Healthy Males (venous)	1	12	0.14	0.5-0.6
Perioperative hypertension (arterial)	0.4	15	0.05	0.2
Perioperative hypertension (venous)	0.9	5.4	0.081	0.14
Perioperative hypertension (arterial)	0.5	3.4	0.045	0.03

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

#### **Absorption**

After intravenous administration, the bioavailability of clevidipine is 100%.

#### **Distribution**

Clevidipine 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**

Clevidipine is rapidly metabolized 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 metabolites are the carboxylic acid metabolite and formaldehyde formed by hydrolysis of the ester group. The carboxylic acid metabolite is inactive as an anti-hypertensive. This metabolite is further metabolized by glucuronidation or oxidation to the corresponding pyridine derivative.

*In vitro* studies show that clevidipine and its metabolites at the concentrations achieved in clinical practice will not inhibit or induce any CYP enzyme.

#### **Elimination**

The clearance of the primary dihydropyridine metabolite is 0.03 L/h/kg and the terminal half life is approximately 9 hours.

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

## Special Populations and Conditions

- **Pediatrics:** Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** There is no significant pharmacokinetic association between clevidipine and age.
- **Sex:** There is no significant pharmacokinetic association between clevidipine and sex.
- **Pregnancy and Breast-feeding:** The pharmacokinetics of clevidipine in those who are pregnant or breast-feeding have not been evaluated.
- **Genetic Polymorphism:** There is no significant pharmacokinetic association between clevidipine and genetic polymorphisms.
- **Ethnic Origin:** There is no significant pharmacokinetic association between clevidipine and ethnic origin.
- **Hepatic Insufficiency:** There is no significant pharmacokinetic association between clevidipine and liver function. Clevidipine is not eliminated through hepatic pathways.
- **Renal Insufficiency:** There is no significant pharmacokinetic association between clevidipine and kidney function. Clevidipine is not eliminated through renal pathways. The major metabolite of clevidipine is eliminated via the kidney but has no pharmacologic activity.
- **Obesity:** The pharmacokinetics of clevidipine in patients with obesity have not been evaluated.

## 11 STORAGE, STABILITY AND DISPOSAL

The shelf-life is 30 months when stored at 2°C to 8°C packaged in the marketing packs of 100 mL or 50 mL glass vials sealed with grey bromobutyl stoppers and capped with aluminum overseals. Each vial is placed within a carton in order to protect it from light until administration. Do not freeze.

## 12 SPECIAL HANDLING INSTRUCTIONS

Vials in cartons may be transferred to 25°C (USP controlled room temperature) for a period not to exceed 2 months. Upon transfer to room temperature, mark vials in cartons "This product was removed from the refrigerator on \_\_/\_\_/\_\_ date. It must be used or discarded 2 months after this date or the labelled expiration date (whichever date comes first)." Do not return to refrigerated storage after beginning room temperature storage.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

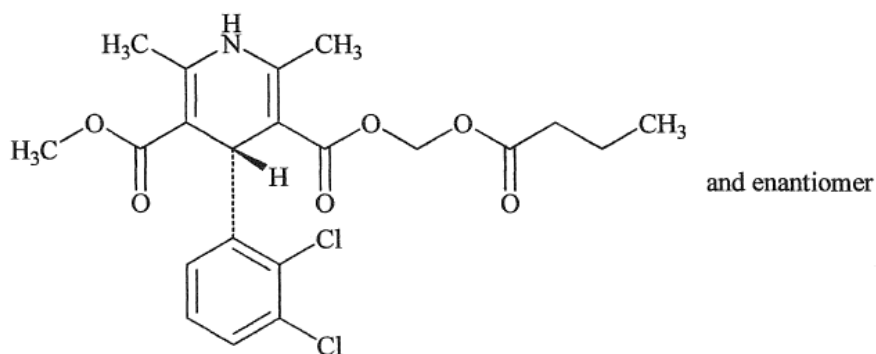
Proper name: clevidipine

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

Molecular formula and molecular mass: C<sub>21</sub>H<sub>23</sub>Cl<sub>2</sub>NO<sub>6</sub>, 456.3 g/mol

Structural formula:





Physicochemical properties: White to off-white solid, which is practically insoluble in water, sparingly soluble in 99.5% ethanol, and slightly soluble in soybean oil.

Two polymorphic forms occur. Polymorph A is the predominant form, which melts at 138°C.

Clevidipine is a racemic mixture of (+)-S and (-)-R enantiomers.

pH of the oil-in-water emulsion formulation: 6.0 to 8.0.

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

**Table 5 Summary of patient demographics for clinical trials in peri-operative hypertension**

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
ESCAPE-1	Double-blind, randomized, parallel, placebo-controlled, multicenter trial in cardiac surgery patients – preoperative	Starting IV infusion rate of 0.4 mcg/kg/min, titrating upward, as tolerated, in doubling increments every ~90 sec up to 3.2 mcg/kg/min for ≥30 to ≤60 min	105 53 clevidipine 52 placebo	Clevidipine: 68.0 (43-82) Placebo: 61.0 (40-82)	Clevidipine: 16 female, 37 male Placebo: 16 female, 36 male
ESCAPE-2	Double-blind, randomized, parallel, placebo-controlled, multicenter trial in cardiac surgery patients – postoperative	Starting IV infusion rate of 0.4 mcg/kg/min, titrating upward, as tolerated, in doubling increments every ~90 sec up to 3.2 mcg/kg/min for ≥30 to ≤60 min	110 61 clevidipine 49 placebo	Clevidipine: 66.0 (27-83) Placebo: 62.0 (40-83)	Clevidipine: 14 female, 47 male Placebo: 11 female, 38 male

CLEVIPREX was evaluated in two double-blind, randomized, parallel, placebo-controlled, multicenter

trials of cardiac surgery patients - preoperative use in ESCAPE-1 (n=105) and postoperative use in ESCAPE-2 (n=110). Patients were undergoing coronary artery bypass grafting, with or without valve replacement. Inclusion in ESCAPE-1 required a systolic pressure  $\geq 160$  mmHg. In ESCAPE-2, the entry criterion was systolic pressure of  $\geq 140$  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 and 47% patients older than age 65.

CLEVIPREX was infused in ESCAPE-1 preoperatively for 30 minutes, until treatment failure, or until induction of anesthesia, 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.

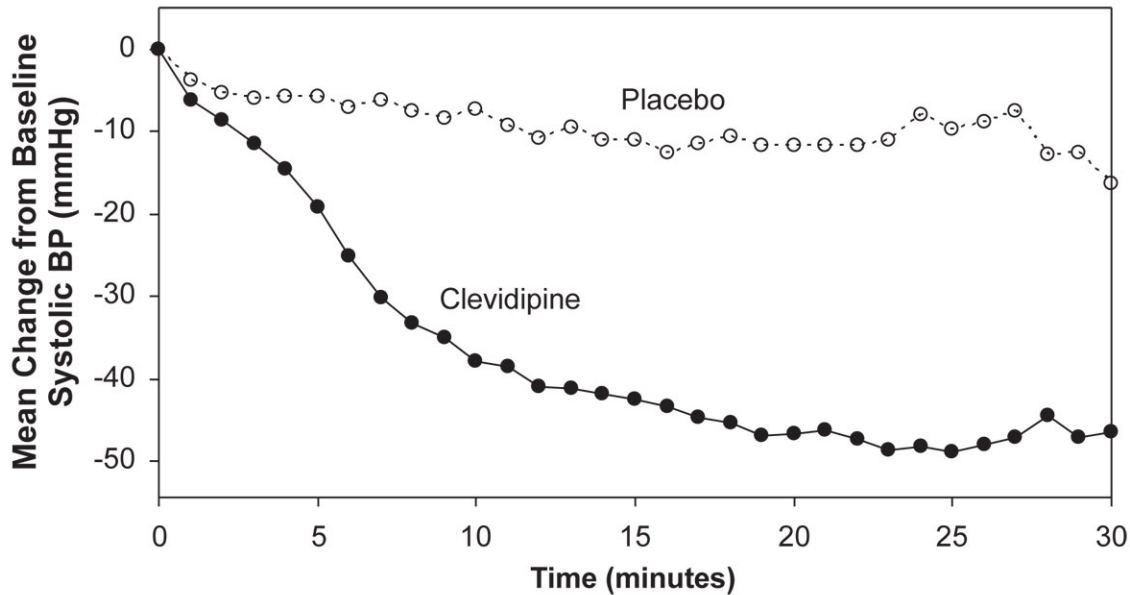
In both studies infusion of CLEVIPREX was started at a dose of 1 to 2 mg/hour and was titrated upwards, as tolerated, in doubling increments every 90 seconds up to an infusion rate of 16 mg/hour in order to achieve the desired blood pressure-lowering effect. At doses above 16 mg/hour increments were 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.

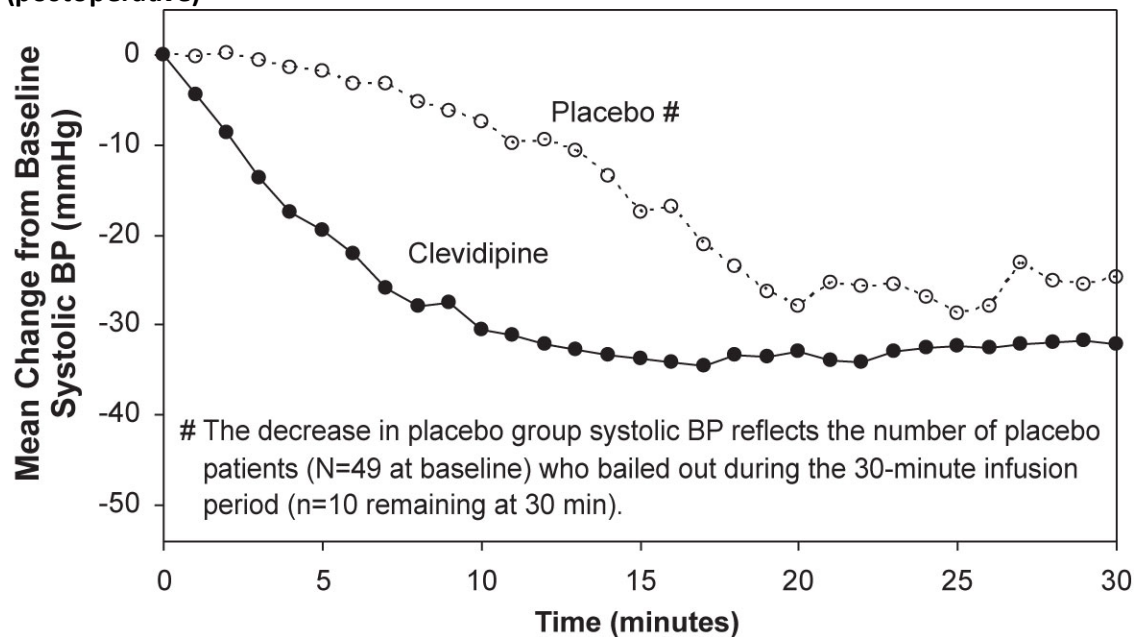
## 14.2 Study Results

CLEVIPREX lowered blood pressure within 2 to 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 [Figure 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)**



## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:** In a 4-week study in rats, clevidipine was infused continuously at daily dose levels of 23, 39, and 66 mg/kg. The no-observed-adverse-effect level (NOAEL) was 23 mg/kg/day at a rate of 0.92 mL/kg/hour, approximately half the maximum recommended human dose (MRHD) of 504 mg/day (21 mg/h x 24 hours; 8.4 mg/kg/day for a patient with a body weight of 60 kg) on a body surface area basis. Changes associated with clevidipine were increased water consumption and urine output and increased adrenal (males) and ovary weights at the 39 and 66 mg/kg/day dose levels. Organ weight changes were without histopathological correlates and were reversible in recovery females. In a 4-week study in dogs, clevidipine was infused 12 hour/day at daily dose levels of 16, 32, and 66 mg/kg. The NOAEL was 16 mg/kg/day at an infusion rate of 1.32 mg/kg/hour, approximately equivalent to the MRHD on a body surface area basis. Pharmacologically related increases in heart rate were observed at all dose levels with a decrease in PR and QT intervals at the highest dose levels (32 and 66 mg/kg/day). This effect was more significant after the first dose than at the end of the study and is considered a reflex response to clevidipine-induced decreased blood pressure in normal dogs. Mean testes weights were low at all dose levels, but there were no microscopic changes that indicated a toxic effect on the testes. Spleen and adrenal weights were higher at the 32 and 66 mg/kg/day and 66 mg/kg/day dose levels, respectively. A marginal increased frequency of injection site changes, including thrombosis and phlebitis, appeared clevidipine related.

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

**Genotoxicity:** Clevidipine displayed a positive genotoxic potential *in vitro* in the Ames test, the mouse

lymphoma thymidine kinase locus assay, and in the chromosomal aberration assay, but not in the *in vivo* mouse micronucleus test. Formaldehyde, a metabolite of clevidipine, a known genotoxicant *in vitro* and a probable human carcinogen, appears to be at least partially responsible for the positive *in vitro* results.

**Reproductive and Developmental Toxicology:** There were no adverse effects on fertility or mating behaviour of male rats with clevidipine doses of up to 55 mg/kg/day, approximately equivalent to the MRHD of 504 mg/day (21 mg/h 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 (about 1/4 the MRHD); however, doses of up to 55 mg/kg/day did not affect mating or fertility.

When pregnant rats were dosed with clevidipine during late gestation and early lactation (terminating on day 4 post-partum), there were dose-related increases in mortality, length of gestation, and prolonged parturition at dose levels as low as 13 mg/kg/day about 1/4 the MRHD of 504 mg/day (21 mg/h x 24 hours) on a body surface area basis. When offspring of these dams were mated, they had a conception rate lower than that of controls. Clevidipine crosses the placental membrane in this species and doses of 35 or more mg/kg/day (about 0.7 times the MRHD) administered during organogenesis adversely affected fetal survival. Fetal survival was also adversely affected when pregnant rabbits were treated during organogenesis with 55 mg/kg/day (about twice the MRHD) on a body surface area basis.

Increased post-implantation losses and dose-related decreases in ossification were seen in both rats and rabbits. In rats, a reduction in ossification of paws was observed that included partially ossified metacarpals, metatarsals, and phalanges suggesting developmental retardation. Renal pelvic cavitation was also observed. In addition, malrotations of a hind limb were observed that were not considered related to skeletal alterations.

Rabbits exhibited a reduction in ossification of supraoccipital bones and sternbrae and unossified heads of long limb bones. In addition, an increase in fused and/or misaligned sternbrae was observed. These effects are similar to changes reported with other calcium channel antagonists.

**Juvenile Toxicity:** There were no adverse effects on sexual maturation and reproductive performance of female and male juvenile rats treated with clevidipine doses of 10, 20, or 40 mg/kg administered over 5 consecutive days by intraperitoneal injection during developmental intervals representing postnatal days (PND) 10-14, 16-20, 21-25, and 26-30 or by 2-hour IV infusion in older, more developmentally mature rats (PND 32-36). After a treatment-free period until they were approximately 85 days of age, animals were paired for mating. The growth, survival, and clinical condition of F1 pups was unaffected by F0 test article administration at the same dose levels and developmental intervals. Bilateral small testes and epididymes were observed in 1 male in the 20 mg/kg PND 16-20 group and 2 males in the 40 mg/kg PND 21-25 group. The NOAEL for systemic and reproductive toxicity was 10 mg/kg.

In a subsequent juvenile toxicity study, there were no adverse findings in juvenile male rats dosed with 10, 20, or 40 mg/kg clevidipine by intraperitoneal injection during PND 21-25. There were no test article-related findings on spermatogenesis parameters or microscopic findings in the testes. The NOAEL for systemic toxicity and spermatogenesis parameters was 40 mg/kg/day.

## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrCLEVIPREX**

#### **Clevidipine Injection**

Read this carefully before you are given **CLEVIPREX**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CLEVIPREX**.

#### **What is CLEVIPREX used for?**

CLEVIPREX is used in adults to manage increases in blood pressure during surgery.

#### **How does CLEVIPREX work?**

CLEVIPREX belongs to a group of medicines called “calcium channel blockers” or “calcium antagonists”. It relaxes the arteries, which allows blood to flow freely through them. This helps to lower blood pressure.

#### **What are the ingredients in CLEVIPREX?**

Medicinal ingredients: clevidipine

Non-medicinal ingredients: edetate disodium, glycerin, oleic acid, purified egg yolk phospholipids, sodium hydroxide (for pH adjustment), soybean oil, and water for injection

#### **CLEVIPREX comes in the following dosage forms:**

Injectable emulsion: 0.5 mg/mL

#### **Do not use CLEVIPREX if:**

- you have an allergy to clevidipine or to any other ingredients in CLEVIPREX or its container. This includes soybean, soybean oil or soy products, eggs or egg products, peanuts or peanut products.
- you have a condition where you have extremely high levels of fat in your blood (e.g., pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis accompanied with hyperlipidemia).
- you have severe aortic stenosis (narrowing of the opening of the biggest artery in the body).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CLEVIPREX. Talk about any health conditions or problems you may have, including if you:**

- Have or have had heart failure or low blood pressure. CLEVIPREX can worsen these conditions.

- Have a tumour of the gland on top of the kidney (adrenal gland) that causes high blood pressure (pheochromocytoma).

**Other warnings you should know about:**

**CLEVIPREX can cause serious side effects, including:**

- **Hypotension** (low blood pressure)
- **Tachycardia** (abnormally fast heartbeat)

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

**Pregnancy:** It is not known if CLEVIPREX can harm an unborn baby. Tell your healthcare professional if you are pregnant or think you may be pregnant before your treatment with CLEVIPREX. You and your healthcare professional will decide if you should be given CLEVIPREX during pregnancy.

**Breastfeeding:** It is not known if CLEVIPREX can pass into your breast milk and harm your baby. Tell your healthcare professional that you are breastfeeding.

**Check-ups and testing:** Your healthcare professional will monitor your health during and after your treatment with CLEVIPREX. They will check your blood pressure and your heart rate.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

Drug interactions are unlikely to occur with CLEVIPREX. This is due to the way the body processes it.

**How to take CLEVIPREX:**

CLEVIPREX will be given to you by a healthcare professional in a hospital or medical office. It will be injected into a vein.

**Usual dose:**

Your healthcare professional will decide what dose of medication you will receive and for how long. This will depend on your blood pressure and how you respond to CLEVIPREX.

**Overdose:**

Symptoms of an overdose with CLEVIPREX include:

- mild reddening of the skin;
- low blood pressure;
- abnormally fast heartbeat.

If you think you, or a person you are caring for, have been given too much CLEVIPREX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**What are possible side effects from using CLEVIPREX?**

These are not all the possible side effects you may have when taking CLEVIPREX. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache
- dizziness
- trouble sleeping or staying asleep
- nausea
- fever

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
<b>Hypotension</b> (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when taken with medicines called beta-blockers).		√	
<b>Tachycardia</b> (abnormally fast heartbeat)		√	
<b>Hypertension</b> (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitation.		√	
<b>UNCOMMON</b>			
<b>Acute kidney failure</b> (severe kidney problems): confusion, itchiness or rashes, puffiness in your face and hands, swelling in your feet or ankles, urinating less or not at all, weight gain.		√	
<b>Atrial fibrillation</b> (abnormal heart rhythm which is rapid and		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
irregular): chest discomfort with unpleasant awareness of your heartbeat, faintness, shortness of breath, weakness.			
<b>Atelectasis</b> (collapse of part or all of a lung): shortness of breath, rapid, shallow breathing, wheezing, cough, chest pain, skin and lips turning blue.		√	
<b>UNKNOWN FREQUENCY</b>			
<b>Allergic reaction:</b> difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives, rash, or swelling of the face, lips, tongue or throat.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*



**Storage:**

- Store vials in the carton at 2°C to 8°C. Vials in the carton may be stored for up to 2 months at room temperature (25°C). Do not freeze or re-refrigerate. Leave vials in carton to protect from light until use.
- Vials must be discarded 2 months after the date they have been removed from the refrigerator or after the expiration date (whichever date comes first).

**If you want more information about CLEVIPREX:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); or by calling the importer Methapharm Inc. at 1-800-287-7686 ext. 7804.

This leaflet was prepared by Chiesi Farmaceutici S.p.A., Parma, Italy.

Last Revised: June 22, 2022