SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

CLEVIPREX® 0,5 MG/ML EMULSION FOR INJECTION

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml emulsion for injection contains 0,5 mg clevidipine.

One vial of 50 mL of emulsion contains 25 mg of clevidipine.

One vial of 100 mL of emulsion contains 50 mg of clevidipine.

Excipients with known effect

Cleviprex contains 10 g/20 g soya-bean oil refined per 50 mL/100 mLvial.

Contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for injection

White opaque, oil-in-water emulsion.

pH: 6,0 – 8,0. Osmolarity: 341 mOsmols/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cleviprex is indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable.

4.2 Posology and method of administration

Adults/Elderly

Cleviprex is intended for intravenous use. Titrate medicine to achieve the desired blood pressure reduction. Individualise dosage depending on the blood pressure to be obtained and the response of the patient. Blood pressure and heart rate must be monitored continually during the 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 infusion is stopped.

Initial dose: Initiate the intravenous infusion of Cleviprex at 4 ml/h (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 8-12 ml/h (4-6 mg/h).

Maximum dose: Most patients in clinical studies were treated with doses of 32 ml/h (16 mg/h) or less.

The maximum recommended dose is 64 ml/h (32 mg/h). Patients with severe hypertension may require doses up to 64 ml/h (32 mg/h), but there is limited experience with this dose rate. No more than 1000 ml of Cleviprex infusion is recommended per 24-hour period due to the associated lipid load. There is limited experience with Cleviprex infusion durations beyond 72 hours at any dose.

Transition to an oral antihypertensive medicine:

Discontinue Cleviprex or titrate downward while appropriate oral therapy is established. When an oral antihypertensive medicine is being instituted, consider the lag time of onset of the oral medicine's effect. Continue blood pressure monitoring until desired effect is achieved. Discontinuation of Cleviprex leads to a reduction in antihypertensive effects within 5 to 15 minutes.

Instructions for use

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.

Clevidipine 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 should be administered via a vented spike and infusion device.

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.

Cleviprex should not be administered in the same intravenous line as other medications.

Hepatic Impairment

Data regarding the dosage regimen in patients with hepatic impairment is limited and has not been specifically studied. No dose adjustment is required in patients with hepatic impairment.

Renal Impairment

Data regarding the dosage regimen in patients with renal impairment is limited and has not been specifically studied. The recommended titration of Cleviprex does not need to be adjusted in patients with renal impairment.

Paediatric population

The safety and efficacy of Cleviprex in children aged 0 to 18 years old has not yet been established. Cleviprex should not be used in children aged less than 18 years

Patients on other lipid-based therapies.

Cleviprex contains approximately 0,2 g of lipid per ml (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.

4.3 Contraindications

Hypersensitivity to the active substance, soybeans, soya-bean oil refined, soy products, peanut, eggs or egg products or to any of the other excipients listed in section 6.1.

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

Cleviprex must 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

Use strict aseptic technique and discard any unused product within 12 hours of stopper puncture. Failure to practice appropriate aseptic technique may lead to contamination of infused product and the potential for systemic infection

Hypotension and reflex tachycardia

Rapid pharmacologic reductions in blood pressure may produce systemic hypotension and reflex tachycardia. If either occurs with Cleviprex, consider decreasing the dose by half or stopping the infusion.

Patients with aortic stenosis, hypertrophic obstructive cardiomyopathy, mitral stenosis, aortic dissection or pheochromocytoma have not been studied in clinical trials with Cleviprex.

Hypoxia

Cleviprex should not be used in patients with uncorrected critical aortic stenosis because excessive afterload reduction can reduce myocardial oxygen delivery. For patients undergoing surgery to relieve their stenosis with a replacement valve, Cleviprex may be useful in the post- operative period if the ability to compensate for decreases in blood pressure has been restored.

Patients with hypertrophic obstructive cardiomyopathy and mitral stenosis may also be at risk of reduced oxygen delivery.

Cleviprex should be used with caution in patients who cannot increase their heart rate adequately to compensate for reduced blood pressure such as those with left bundle-branch block or primary ventricular pacing.

There is limited data for use of Cleviprex in acute myocardial infarction or acute coronary syndrome.

Cleviprex contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Cleviprex contains soya-bean oil refined.

Contains 10 g/20 g soya-bean oil refined per 50 ml/100 ml vial. Hypersensitivity to soya-bean oil refined is a contraindication.

4.5 Interaction with other medicinal products and other forms of interaction.

No interaction studies have been performed as pharmacokinetic medicine interactions are unlikely given Cleviprex is metabolised by hydrolysis *in vivo*.

Inhibition of CYP isoforms was detected in *in vitro* studies at concentrations equivalent to at least 10 times the highest concentration typically seen in the clinic. At the doses recommended, Cleviprex and its major dihydropyridine metabolite do not have the potential for inhibiting or inducing any CYP enzyme.

Patients receiving oral or IV anti-hypertensive medicines, including betablockers, while on Cleviprex should be observed closely for increased anti-hypertensive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Rats dosed with Cleviprex during late gestation and lactation showed a dose-related increase in mortality, length of gestation, and prolonged parturition at dose levels of 13,35, and 55 mg/kg/day.

Cleviprex has been shown to cross the placenta in rats. No evidence of embryo-foetal malformation was found with continuous IV infusion of Cleviprex during the period of organogenesis at doses up to 13 mg/kg/day in pregnant rats and 35 mg/kg/day in pregnant rabbits (2,8 to 7,6 times the expected human dose of 16 mg/hour). Embryo-foetal toxicity

(intrauterine deaths, slightly reduced foetal weight, retarded skeletal development, abortion, and embryo lethality) was seen with continuous IV infusion of Cleviprex during the period of organogenesis at 35 mg/kg/day in pregnant rats and at 55 mg/kg/day in pregnant rabbits (7,6 to12 times the expected maximum human dose of 16 mg/hour). 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 sternebrae and unossified heads of longlimb bones. In addition, an increase in fused and/or misaligned sternebrae were observed. There was no evidence that Cleviprex was teratogenic at the highest dose levels studied in pregnant rats and rabbits.

Cleviprex should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is unknown whether Cleviprex is excreted in human breast milk. The excretion of Cleviprex in milk has not been studied in animals. Cleviprex should not be used during breastfeeding

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 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 (about 1/4th the MRHD); however, doses of up to 55 mg/kg/day did not affect mating performance or fertility.

4.7 Effects on ability to drive and use machines

Cleviprex has moderate influence on the ability to drive and use machines.

Cleviprex may cause dizziness which could interfere with the ability to drive or operate machinery; however, patients receiving Cleviprex will be confined to hospital for the duration of treatment.

4.8 Undesirable effects

Cleviprex has been evaluated for safety in 1,423 hypertensive patients. Infusion rate was evaluated for 1,326 patients among whom 6 % were treated with the mean dose of >32 ml/h (16 mg/h) and up to the maximum recommended therapeutic dose of 64 ml/h (32 mg/h).

Continuous infusion duration was evaluated for 1,380 patients 20 % of whom 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 clinical studies, a total of 2,5 % of patients receiving Cleviprex experienced oxygen saturation decrease (reported as hypoxia).

In all Phase III clinical trials on cardiac surgical patients, the incidence of atrial fibrillation in patients treated with Cleviprex was 32.8%.

The incidence of sinus tachycardia in perioperative patients treated with Cleviprex was 25,5 %.The incidence of hypotension in perioperative patients treated with Cleviprex was 15,1%.

The adverse reactions (Table 1: Perioperative 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 as MedDRA preferred term by system organ class and absolute frequency.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions in perioperative hypertension patients

System organ class	**Adverse reaction**	**Frequency category**
Cardiac disorders	Atrial fibrillation	Common
	Sinus tachycardia	Common
	Atrial flutter	Uncommon
	Tachycardia	Uncommon
	Cardiac failure congestive	Uncommon
	Bradycardia	Uncommon
	Atrioventricular block complete	Uncommon
	Bundle branch block	Uncommon
Gastrointestinal disorders	Constipation	Uncommon
	Nausea	Uncommon
	Vomiting	Uncommon
	Ileus	Rare
General disorders and administration site conditions	Oedema	Common
	Chest pain	Common
Investigations	Increased blood triglycerides	Very rare
Nervous system disorders	Dizziness	Uncommon
	Headache	Uncommon

Renal and urinary disorders	Acute kidney injury	Common
Respiratory, thoracic and mediastinal disorders	Hypoxia	Common
	Pulmonary congestion	Uncommon
Vascular disorder	Hypotension	Common

In clinical studies in patients in non-perioperative settings (n=294) the following additional adverse reactions were seen in patients treated with Cleviprex: hypersensitivity (uncommon), myocardial infarction (uncommon), cardiac arrest (uncommon), syncope (uncommon), dyspnea (uncommon), flushing (common), feeling hot (common) and polyuria (common).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

An overdose of Cleviprex may result in tachycardia or excessive reduction in blood pressure. If either occurs with Cleviprex, consider decreasing the dose by half or stopping the infusion. Discontinuation of Cleviprex leads to a reduction in antihypertensive effects within 5 to 15 minutes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dihydropyridine derivatives,

ATC code:C08CA16

Pharmacological Classification: A 7.1.3 Other hypotensives

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: Clevidipine is titrated to the desired reduction in blood pressure.

In the perioperative patient population, clevidipine produces a 4-5 % reduction in systolic blood pressure (SBP) within 2-4 minutes after starting a 0,4 microgram/kg/min infusion (approximately 2-4 ml/h [1-2 mg/h]). In studies 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 of continuous infusion, in patients that were not transitioned to other antihypertensive therapies, there was some evidence of rebound hypertension following clevidipine discontinuation.

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

An increase in heart rate can be a normal response to rapid decreases in blood pressure; in some patients the heart rate response may be pronounced.

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

Clevidipine 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 and SBP≥140 mmHg, respectively). The mean continuous infusion duration was 30 minutes (min 4 minutes, max 1 hour). The primary endpoint was ‘bailout’ defined by premature and permanent discontinuation of study medicine, with patients transferred to alternative open-label therapy.

In greater than 90 % of patients treated with clevidipine, blood pressure was lowered by ≥15 % within 30 minutes. Bailout rates were 7,5% and 8,2% in ESCAPE-1 and ESCAPE-2, respectively.

The blood-pressure–lowering effect with clevidipine 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 (clevidipine – 1,6 %) and insomnia (clevidipine – 1,6 %).

In three Phase 3, actively controlled, open-label clinical trials (ECLIPSE), 1,506 patients were randomised and received clevidipine (n=752), nitroglycerine (perioperative, n=278), sodium nitroprusside (perioperative, n=283), or nicardipine (postoperative, n=193).

The mean continuous infusion duration was 4 hours (min 1 minute, max 127 hours). 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.

There was no difference between clevidipine and reference therapies in the incidence of death (2.8% for clevidipine), stroke (1.1% for clevidipine), MI (2.3% for clevidipine) and renal dysfunction (7.9% for clevidipine).

Regarding efficacy, clevidipine significantly reduced blood pressure compared to reference therapies.

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 clevidipine and in those who received comparator agents. The incidence of adverse events leading to study medicine discontinuation in patients with perioperative hypertension receiving clevidipine was 5,9 %.

Essential and severe hypertension

Additional studies have been conducted in patients with essential hypertension, with severe hypertension, in acutely hypertensive patients with acute intracerebral haemorrhage, and in patients with acute heart failure and elevated systolic blood pressure.

Clevidipine was evaluated in a prospective, open-label, single-arm clinical trial (VELOCITY) in 126 patients with severe hypertension (SBP >180 mmHg or diastolic blood pressure [DBP] >115 mmHg). Clevidipine infusion was initiated at 2 mg/h and titrated in doubling increments

every 3 min up to a maximum dose of 32 mg/h, as required to achieve a prespecified target blood pressure range within 30 min. Clevidipine was then continued for a total duration of 18 to 96 hours. The transition to oral antihypertensive therapy was assessed for up to 6 hours following cessation of clevidipine infusion.

The average infusion rate was 9,5 mg/h. The mean duration of clevidipine exposure was 21 hours. Within 30 min after start of clevidipine, 88,9 % (104/117) of patients achieved the target blood pressure range (primary efficacy endpoint), with a median time to target range of 10,9 min and a median dose of 8 mg/hr. The mean decrease in SBP at 30 min was 21,1 %. Within 3 min after the start of clevidipine 1,6 % (2/126) of patients had a SBP decrease below the lower limit of the target range (primary safety endpoint). No concomitant intravenous antihypertensives were needed in 92,3 % (108/117) of patients receiving 18 hours or more of clevidipine infusion. Clevidipine was well tolerated with successful transition to oral antihypertensive therapy in 91,3 % (115/126) of patients.

Clevidipine was evaluated in a prospective, open-label, single-arm clinical trial (ACCELERATE) in 35 patients with intracerebral haemorrhage and acute elevated blood pressure (SBP >160 mmHg). The primary endpoint was the median time to achieve the target SBP (≤ 160 to ≥ 140 mm Hg) within 30 min after clevidipine start.

The average infusion rate was 7,7 mg/hr. The mean duration of clevidipine exposure was 28,3 hours. The median time to achieve the target blood pressure range was 5,5 min (primary efficacy endpoint).

Within 30 min after start of clevidipine, 96,9 % (32/33) of patients achieved the target blood pressure range with clevidipine monotherapy. The mean decrease in SBP at 30 min was 20 %. Clevidipine was well tolerated and adverse events consistent with previous clinical experience.

In a randomized, open label, actively controlled, open-label clinical trial (PRONTO), 104 patients with acute heart failure and hypertension (SBP ≥ 160 mmHg) were randomized and received clevidipine (n=51) or standard of care (SOC, n=53). The co-primary endpoints were the median time to and the percent of patient attaining the target SBP (a minimum 15 % reduction with a range of 20 to 40 mmHg) within 30 min after clevidipine start.

The average infusion rate of clevidipine in the first 30 min was 6.4 mg/hr. The majority of patients treated with SOC received either nitroglycerin (57 %) or nicardipine IV (30 %). Patients treated with clevidipine achieved the target blood pressure more often than patients treated with SOC (70,5 % [31/44] vs 36,6 % [15/41] respectively, p = 0,002), and reached this endpoint sooner (p = 0.0006).

Clevidipine was effective at reducing blood pressure. Patients treated with clevidipine had a greater improvement in dyspnea than patients treated with SOC (p = 0,02). Serious adverse events and mortality were similar between the two groups.

5.2 Pharmacokinetic properties

Clevidipine is rapidly distributed and metabolised. 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.

Distribution: Clevidipine is >99,5 % bound to proteins in plasma at 37 °C. The steady state volume of distribution is 0,17 L/kg in arterial blood.

Metabolism and elimination: 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 metabolites are 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 show that clevidipine and its metabolite at the concentrations achieved in clinical practice do not inhibit or induce any CYP enzyme.

In a clinical study with radiolabelled clevidipine, 83 % of the medicine 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

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Findings in the repeated-dose studies were generally related to the pharmacology of clevidipine and/or the administration of high quantities of lipid vehicle. These effects are considered of little relevance to the shorter-term clinical use.

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 a genotoxic *in vitro* and a probable human carcinogen. However, human *in vivo* exposure to formaldehyde at the maximum clinical doses of clevidipine (64 ml/h [32 mg/h]) is at least several hundred times less than normal daily endogenous formaldehyde generation and is therefore not of clinical concern. 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-bean oil refined

Glycerol

Egg phospholipids

Oleic acid

Disodium edetate

Water for injections

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

30 months refrigerated (2 °C – 8 ºC).

From a microbiological perspective the stopper should be punctured immediately before use and any remaining product discarded after 12 hours.

6.4 Special precautions for storage

Store and transport refrigerated (2 °C – 8 °C). Do not freeze[1].

Keep vial in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

[1]The freezing point of Cleviprex is between -1 °C and 0 °C.

6.5 Nature and contents of container

Single-use, pre-mixed 50 mL and 100 mL, Type I glass vials, sealed with a grey bromobutyl rubber stopper and capped with a flip-off aluminium overseal.

Pack sizes: 10 x 50 mL vials or 10 x 100 mL vials.

Not all vial sizes may be marketed.

6.6 Instructions for disposal and other handling

For single use only.

Lipid filters with a 1,2 micron pore size may be used when administering Cleviprex.

Cleviprex should not be diluted.

Cleviprex should not be administered in the same line as other medications; however, Cleviprex can be administered with the following:

Water for Injection

Sodium Chloride (0,9 %) Injection

Sodium Chloride (0,45 %) Injection

5 % glucose solution

5 % glucose in Sodium Chloride (0,9 %) Injection

5 % glucose in Ringers Lactate Injection

Lactated Ringers Injection

40 meq Potassium Chloride in 0,9 % Sodium Chloride

10 % amino acid

Compatibility may vary between products from different sources and healthcare professionals are advised to carry out appropriate checks when mixing Cleviprex emulsion for injection with other parenteral solutions.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.HOLDER OF CERTIFICATE OF REGISTRATION

Safeline Pharmaceuticals (Pty) Ltd

4845 Rugby Street

Weltevreden Park

South Africa

8. REGISTRATION NUMBER(S)

57/7.1.3/0265

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 November 2023

10. DATE OF REVISION OF TEXT