SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cepedex 0.1 mg/mL solution for injection for dogs and cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains:

Active substance:

Dexmedetomidine hydrochloride	0.1 mg
(equivalent to dexmedetomidine	0.08 mg)

Excipients:

Methyl parahydroxybenzoate (E218)	2.0 mg
Propyl parahydroxybenzoate	0.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

Non-invasive, mildly to moderately painful procedures and examinations which require restraint, sedation and analgesia in dogs and cats.

Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.

Premedication in dogs and cats before induction and maintenance of general anaesthesia.

4.3 Contraindications

Do not use in animals with cardiovascular disorders.
Do not use in animals with severe systemic disease or in animals that are moribund.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

The administration of dexmedetomidine to puppies younger than 16 weeks and kittens younger than 12 weeks has not been studied.

4.5 Special precautions for use

Special precautions for use in animals
Treated animals should be kept warm and at a constant temperature, both during the procedure and recovery.

It is recommended that animals are fasted for 12 hours prior to Cepedex administration. Water may be given.

After treatment, the animal should not be given water or food before it is able to swallow.

Corneal opacities may occur during sedation. The eyes should be protected by a suitable eye lubricant.
To be used with precaution in elderly animals.

The safety of dexmedetomidine has not been established in males intended for breeding.
Nervous, aggressive or excited animals should be given the possibility to calm down before initiation of treatment.

Frequent and regular monitoring of respiratory and cardiac function should be performed. Pulse oximetry may be useful but is not essential for adequate monitoring. Equipment for manual ventilation should be available in case of respiratory depression or apnoea when dexmedetomidine and ketamine are used sequentially to induce anaesthesia in cats. It is also advisable to have oxygen readily available, should hypoxaemia be detected or suspected.

Sick and debilitated dogs and cats should only be premedicated with dexmedetomidine before induction and maintenance of general anaesthesia based on a risk-benefit assessment.

Use of dexmedetomidine as a premedicant in dogs and cats significantly reduces the amount of induction medicinal product required for induction of anaesthesia. Attention should be given during the administration of intravenous induction medicinal products to effect. Volatile anaesthetic requirements for maintenance anaesthesia are also reduced.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Dexmedetomidine is a sedative and sleep-inducing drug. Care should be taken to avoid self-injection.
In case of accidental oral intake or self-injection, seek medical advice immediately and show the package leaflet or the label to the physician but DO NOT DRIVE as sedation and changes in blood pressure may occur.

Pregnant women should administer the product with special caution to avoid self-injection since uterine contractions and decreased foetal blood pressure may occur after accidental systemic exposure.

Avoid skin, eye or mucosal contact; the use of impermeable gloves is advisable. In case of skin or mucosal contact, wash the exposed skin immediately after exposure with large amounts of water and remove contaminated clothes that are in direct contact with skin. In case of eye contact, rinse abundantly with fresh water. If symptoms occur, seek the advice of a physician.

People with known hypersensitivity to the active substance or any of the excipients should administer the veterinary medicinal product with caution.

Advice to physicians: dexmedetomidine is an α2-adrenoceptor agonist, symptoms after absorption may involve clinical effects including dose-dependent sedation, respiratory depression, bradycardia, hypotension, a dry mouth, and hyperglycaemia. Ventricular arrhythmias have also been reported. Respiratory and haemodynamic symptoms should be treated symptomatically. The specific α2-adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonise dexmedetomidine-induced effects.

4.6 Adverse reactions (frequency and seriousness)

By virtue of its α2-adrenergic activity, dexmedetomidine causes a decrease in heart rate and body temperature.

A decrease in respiratory rate may occur in some dogs and cats. Pulmonary oedema has been reported rarely. Blood pressure will increase initially and then return to normal or below normal. Due to peripheral vasoconstriction and venous desaturation in the presence of normal arterial oxygenation, the mucous membranes may appear pale and/or with a blue tinge.

Vomiting may occur 5-10 minutes after injection. Some dogs and cats may also vomit at the time of recovery.

Muscle tremors may occur during sedation.

Corneal opacities may occur during sedation (see also section 4.5).

When dexmedetomidine and ketamine are used sequentially, with a 10-minute interval, cats may occasionally experience atrioventricular (AV)-block or extrasystoles. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. The incidence of hypoxaemia was common in clinical trials, especially within the first 15 minutes of dexmedetomidine-ketamine anaesthesia. Vomiting, hypothermia and nervousness have been reported after such use.

When dexmedetomidine and butorphanol are used concomitantly in dogs, bradypnoea, tachypnoea, an irregular respiratory pattern (20-30 sec apnoea followed by several rapid breaths), hypoxaemia, muscle twitch or tremor or paddling, excitation, hypersalivation, retching, vomiting, urination, skin erythema, a sudden arousal, or prolonged sedation may occur. Brady- and tachyarrhythmias have been

reported. These may include profound sinus bradycardia, first and second degree AV-block, sinus arrest or pause, as well as atrial, supraventricular and ventricular premature complexes.

When dexmedetomidine is used as a premedicant in dogs, bradypnoea, tachypnoea and vomiting may occur. Brady- and tachyarrhythmias have been reported and include profound sinus bradycardia, first and second degree AV-block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and third degree AV-block may be observed in rare cases.

When dexmedetomidine is used as a premedicant in cats, vomiting, retching, pale mucous membranes, and low body temperature may occur. Intramuscular dosing at 40 micrograms/kg bodyweight (bw) (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in first degree AV-block, and rarely resulted in supraventricular premature depolarisations, atrial bigeminy, sinus pauses, second degree AV-block, or escape beats/rhythms.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of dexmedetomidine has not been established during pregnancy and lactation in the target species. Therefore, the use of the product during pregnancy and lactation is not recommended.

4.8 Interaction with other medicinal products and other forms of interaction

The use of other central nervous system depressants is expected to potentiate the effects of dexmedetomidine and therefore an appropriate dose adjustment should be made. Anticholinergics should be used with caution with dexmedetomidine. Administration of atipamezole after dexmedetomidine rapidly reverses the effects and thus shortens the recovery period. Within 15 minutes, dogs and cats are normally awake and standing.

Cats: After administration of 40 micrograms dexmedetomidine/kg bw intramuscularly concurrently with 5 mg ketamine/kg bw to cats, the maximum concentration of dexmedetomidine increased twofold but there was no effect on T_{max}. The mean half-life of elimination of dexmedetomidine increased to 1.6 h and the total exposure (AUC) increased by 50%.

A dose of 10 mg ketamine/kg bw used concurrently with 40 micrograms dexmedetomidine/kg bw may cause tachycardia.

Atipamezole does not reverse the effect of ketamine.

4.9 Amounts to be administered and administration route

The veterinary medicinal product is intended for:

- Dogs: intravenous or intramuscular use.
- Cats: intramuscular use.

The veterinary medicinal product is not intended for repeat injections.

Dexmedetomidine, butorphanol and/or ketamine can be mixed in the same syringe as they have been shown to be pharmaceutically compatible.

The following doses are recommended:

Dogs:
Dexmedetomidine doses are based on body surface area.

For non-invasive, mildly to moderately painful procedures and examinations requiring restraint, sedation and analgesia:

Intravenously: up to 375 micrograms/square metre body surface area.
Intramuscularly: up to 500 micrograms/square metre body surface area.

When administering in conjunction with butorphanol (0.1 mg/kg bw) for deep sedation and analgesia, the intramuscular dose of dexmedetomidine is
300 micrograms/square metre body surface area.

The premedication dose of dexmedetomidine is 125 – 375 micrograms/square metre body surface area, administered 20 minutes prior to induction for procedures requiring anaesthesia. The dose should be adjusted to the type of surgery, length of procedure and patient temperament.

Concomitant use of dexmedetomidine and butorphanol produces sedative and analgesic effects beginning no later than 15 minutes after administration. The peak sedative and analgesic effects are reached within 30 minutes after administration. Sedation lasts for at least 120 minutes post administration and analgesia lasts for at least 90 minutes. Spontaneous recovery occurs within 3 hours.

Premedication with dexmedetomidine will significantly reduce the dose of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol and thiopental was reduced by 30% and 60% respectively. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect. In a clinical study, dexmedetomidine contributed to postoperative analgesia for 0.5 – 4 hours. However, this duration is dependent on a number of variables and further analgesia should be administered in accordance with clinical judgement.

The corresponding doses based on bodyweight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

For non-invasive, mildly to moderately painful procedures and examinations requiring restraint, sedation and analgesia and for premedication						
Dog bodyweight (kg)	**Dexmedetomidine 125 micrograms/m^2**		**Dexmedetomidine 375 micrograms/m^2**		**Dexmedetomidine 500 micrograms/m^2***	
	(mcg/kg)	**(mL)**	**(mcg/kg)**	**(mL)**	**(mcg/kg)**	**(mL)**
2-3	9.4	0.2	28.1	0.6	40	0.75
3.1-4	8.3	0.25	25	0.85	35	1
4.1-5	7.7	0.35	23	1	30	1.5
5.1-10	6.5	0.5	19.6	1.45	25	2
10.1-13	5.6	0.65	16.8	1.9		
13.1-15	5.2	0.75				
15.1-20	4.9	0.85				

*only IM

	For deep sedation and analgesia with butorphanol	
Dog bodyweight (kg)	**Dexmedetomidine 300 micrograms/m^2 intramuscularly**	
	(mcg/kg)	**(mL)**
2-3	24	0.6
3.1-4	23	0.8
4.1-5	22.2	1
5.1-10	16.7	1.25
10.1-13	13	1.5
13.1-15	12.5	1.75

For higher bodyweight ranges, use Cepedex 0.5 mg/mL and its dosing tables.

Cats:
The dose for cats is 40 micrograms dexmedetomidine hydrochloride/kg bw equal to a dose volume of 0.4 mL Cepedex/kg bw when used for non-invasive, mildly to moderately painful procedures requiring restraint, sedation and analgesia.

When dexmedetomidine is used for premedication in cats, the same dose is used. Premedication with dexmedetomidine will significantly reduce the dose of the induction agent required and will reduce volatile anaesthetic requirements for maintenance anaesthesia. In a clinical study, the requirement for propofol was reduced by 50%. All anaesthetic agents used for induction or maintenance of anaesthesia should be administered to effect.

Anaesthesia can be induced 10 minutes after premedication by intramuscular administration of a target dose of 5 mg ketamine/kg bw or by intravenous administration of propofol to effect. Dosing for cats is presented in the following table.

Cat bodyweight (kg)	**Dexmedetomidine 40 micrograms/kg intramuscularly**	
	(mcg/kg)	**(mL)**
1-2	40	0.5
2.1-3	40	1

For higher bodyweight ranges, use Cepedex 0.5 mg/mL and its dosing table.

Dogs and cats
The expected sedative and analgesic effects are reached within 15 minutes after administration and are maintained up to 60 minutes after administration. Sedation may be reversed with atipamezole (see section 4.10). Atipamezole should not be administered prior to 30 minutes following ketamine administration.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Dogs:
In cases of overdose, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate dose of atipamezole is 10 times the initial dose of dexmedetomidine (micrograms/kg bw or micrograms/square metre body surface area). The dose volume of atipamezole at the concentration of 5 mg/mL is one fifth (1/5) of the dose volume of Cepedex 0.1 mg/mL that was given to the dog, regardless of route of administration of Cepedex.

Cats:
In cases of overdose, or if the effects of dexmedetomidine become potentially life-threatening, the appropriate antagonist is atipamezole, administered by intramuscular injection, at the following dose: 5 times the initial dose of dexmedetomidine in micrograms/kg bw. The dose volume of atipamezole at the concentration of 5 mg/mL is one-tenth (1/10) the volume of Cepedex 0.1 mg/mL that was given to the cat.

After concurrent exposure to an overdose of dexmedetomidine (3 times the recommended dose) and 15 mg ketamine/kg bw, atipamezole can be administered at the recommended dose level for reversal of effects induced by dexmedetomidine.

4.11 Withdrawal period(s)

Not applicable

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Psycholeptics, hypnotics and sedatives.
ATCvet code: QN05CM18

5.1 Pharmacodynamic properties

Cepedex contains dexmedetomidine as the active substance, which produces sedation and analgesia in dogs and cats. The duration and depth of the sedation and analgesia are dose-dependent. At maximal effect, the animal is relaxed, recumbent and does not respond to external stimuli.

Dexmedetomidine is a potent and selective α2-adrenoceptor agonist that inhibits the release of noradrenaline from noradrenergic neurons. Sympathetic neurotransmission is prevented and the level of consciousness decreases. Reduced heart rate and temporary AV-block can be seen after administration of dexmedetomidine. Blood pressure decreases to normal or below normal levels after

an initial increase. Respiration rate can occasionally decrease. Dexmedetomidine also induces a number of other α2-adrenoceptor-mediated effects, which include piloerection, depression of motor and secretory functions of the gastrointestinal tract, diuresis and hyperglycaemia.

A slight decrease in temperature may be observed.

5.2 Pharmacokinetic particulars

As a lipophilic compound, dexmedetomidine is well absorbed after intramuscular administration. Dexmedetomidine is also rapidly distributed in the body and penetrates the blood-brain barrier readily. According to studies in rats, the maximum concentration in the central nervous system is several times that of the corresponding concentration in plasma. In the circulation, dexmedetomidine is largely bound to plasma proteins (>90%).

Dogs: After an intramuscular dose of 50 micrograms/kg bw a maximum concentration in plasma of about 12 nanograms/ml is reached after 0.6 hours. The bioavailability of dexmedetomidine is 60% and the apparent volume of distribution (Vd) is 0.9 L/kg bw. The elimination half-life ($t_{1/2}$) is 40-50 minutes.

Major biotransformations in the dog include hydroxylation, glucuronic acid conjugation and N- methylation in the liver. All known metabolites lack pharmacological activity. Metabolites are excreted mainly in the urine and to a lesser extent in the faeces. Dexmedetomidine has a high clearance and its elimination depends on the hepatic blood flow. A prolonged elimination half-life is therefore expected with overdoses or when dexmedetomidine is co-administered with other substances, which affect hepatic circulation.

Cats: After a 40 micrograms/kg bw intramuscular dose the C_{max} is 17 ng/mL. The maximum plasma concentration is reached about 0.24 h after intramuscular administration. The apparent volume of distribution (Vd) is 2.2 L/kg bw and the elimination half-life $t_{1/2}$) is one hour.

Biotransformations in the cat occur by hydroxylation in the liver. Metabolites are excreted mainly in the urine (51% of the dose), and to a lesser extent in the faeces. As in dogs dexmedetomidine has a high clearance in cats and its elimination depends on the hepatic blood flow. A prolonged elimination half-life is therefore expected with overdoses or when dexmedetomidine is co-administered with other substances, which affect hepatic circulation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate
Sodium chloride
Sodium hydroxide (E524) (for pH adjustment)
Hydrochloric acid (E507) (for pH adjustment)
Water for injections

6.2 Major incompatibilities

None known.

Dexmedetomidine is compatible with butorphanol and ketamine in the same syringe at least for two hours.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 4 years
Shelf-life after first opening the immediate packaging: 56 days.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Colourless Type I glass vials of 5 mL and 10 mL closed with a coated bromobutyl rubber stopper and aluminium cap in a carton box.

Carton box pack sizes:
1 vial of 5 mL
1 or 5 vials of 10 mL

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CP Pharma Handelsgesellschaft mbH
Ostlandring 13
31303 Burgdorf
Germany

8. MARKETING AUTHORISATION NUMBER

Vm 20916/5000

9. DATE OF FIRST AUTHORISATION

13 December 2016

10. DATE OF REVISION OF THE TEXT

February 2022

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be supplied only on veterinary prescription.

Approved 09 February 2022