

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. STATEMENT OF THE MRLs**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

CP-Pharma Handelsgesellschaft mbH
Ostlandring 13
31303 Burgdorf
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box (0.1 mg/mL)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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



2. STATEMENT OF ACTIVE SUBSTANCES

1 mL contains:

Dexmedetomidine hydrochloride	0.1 mg
(equivalent to dexmedetomidine	0.08 mg)

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

5 mL
10 mL
5 x 10 mL

5. TARGET SPECIES

Dogs and cats

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Dogs: intravenous or intramuscular use.
Cats: intramuscular use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

α -2 agonists can cause severe adverse reaction. See package leaflet for user warnings.

10. EXPIRY DATE

EXP:
Shelf-life after first opening the container: 56 days.
Once broached use by:

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CP Pharma Handelsgesellschaft mbH
Ostlandring 13
31303 Burgdorf
Germany

16. MARKETING AUTHORISATION NUMBER(S)

Vm 20916/5000

17. MANUFACTURER'S BATCH NUMBER

Lot.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Glass vials of 5 or 10 mL (0.1 mg/mL)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cepedex 0.1 mg/mL injection
dexmedetomidine hydrochloride



2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

0.1 mg/mL

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

5 mL
10 mL

4. ROUTE(S) OF ADMINISTRATION

Dogs: IM, IV
Cats: IM

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Once broached use by:

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

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

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:

CP-Pharma Handelsgesellschaft mbH
Ostlandring 13
31303 Burgdorf
Germany

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

1 mL contains:

Active substance:

Dexmedetomidine hydrochloride	0.1 mg
(equivalent to dexmedetomidine	0.08 mg)

Excipients:

Methyl parahydroxybenzoate (E 218)	2.0 mg
Propyl parahydroxybenzoate	0.2 mg

Clear, colourless solution for injection.

4. INDICATION(S)

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.

5. 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.

6. ADVERSE REACTIONS

By virtue of its α_2 -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 the section on Special precautions for the use in animals).

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).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs and cats.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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/m²		Dexmedetomidine 375 micrograms/m²		Dexmedetomidine 500 micrograms/m²*	
	(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 intramuscularly

For deep sedation and analgesia with butorphanol		
Dog bodyweight (kg)	Dexmedetomidine 300 micrograms/m² 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.

9. ADVICE ON CORRECT ADMINISTRATION

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 12 *overdose*). Atipamezole should not be administered prior to 30 minutes following ketamine administration.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Shelf-life after first opening the immediate packaging: 56 days.

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

Do not use this veterinary medicinal product after the expiry date which is stated on the package after EXP.

The expiry date refers to the last day of that month.

12. SPECIAL WARNING(S)

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.

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 α 2-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 α 2-adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonise dexmedetomidine-induced effects.

Use during pregnancy and lactation:

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.

Interactions 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.

Overdose (symptoms, emergency procedures, antidotes):

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 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.

Incompatibilities:

None known.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCTS OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Medicines should not be disposed of via wastewater or household waste. Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

15. OTHER INFORMATION

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.

Cardboard box pack sizes:

1 vial of 5 mL

1 or 5 vials of 10 mL

Not all pack sizes may be marketed.

Approved 09 February 2022

