

**ANNEX I**  
**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 (E 218)	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 case of known 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 insert 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: Cepedex is an  $\alpha_2$ -adrenoreceptor 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  $\alpha_2$ -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize dexmedetomidine-induced effects.

## 4.6 Adverse reactions (frequency and seriousness)

By virtue of its  $\alpha_2$ -adrenergic activity, dexmedetomidine causes a decrease in heart rate and body temperature.

In some dogs and cats, a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. 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 AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into 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, 1<sup>st</sup> and 2<sup>nd</sup> 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, 1<sup>st</sup> and 2<sup>nd</sup> degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3<sup>rd</sup> 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 (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1<sup>st</sup> degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2<sup>nd</sup> degree atrioventricular 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 used concurrently with 40 micrograms dexmedetomidine/ kg 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) 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 body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

<b>Dog Weight (kg)</b>	<b>Dexmedetomidine 125 micrograms/m<sup>2</sup></b>		<b>Dexmedetomidine 375 micrograms/m<sup>2</sup></b>		<b>Dexmedetomidine 500 micrograms/m<sup>2</sup>*</b>	
	<b>(mcg/kg)</b>	<b>(ml)</b>	<b>(mcg/kg)</b>	<b>(ml)</b>	<b>(mcg/kg)</b>	<b>(ml)</b>
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

<b>For deep sedation and analgesia with butorphanol</b>		
<b>Dog Weight (kg)</b>	<b>Dexmedetomidine 300 micrograms/m<sup>2</sup> intramuscularly</b>	
	<b>(mcg/kg)</b>	<b>(ml)</b>
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 weight 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.

<b>Cat Weight (kg)</b>	<b>Dexmedetomidine 40 micrograms/kg intramuscularly</b>	
	<b>(mcg/kg)</b>	<b>(ml)</b>
1-2	40	0.5
2.1-3	40	1

For higher weight 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)**

##### 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 meter 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, 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 stimulus.

Dexmedetomidine is a potent and selective  $\alpha_2$ -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  $\alpha_2$ -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 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. 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 coadministered 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 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 coadministered with other substances, which affect hepatic circulation.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Methyl parahydroxybenzoate (E 218)  
Propyl parahydroxybenzoate  
Sodium chloride  
Sodium hydroxide (E 524) (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: 3 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(S)**

EU/2/16/200/001-003

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:13/12/2016

<Date of last renewal:> <{DD/MM/YYYY}> <{DD month YYYY}.>

### **10. DATE OF REVISION OF THE TEXT**

<{MM/YYYY}>

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

### **PROHIBITION OF SALE, SUPPLY AND/OR USE**

Not applicable.

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cepedex 0.5 mg/ml solution for injection for dogs and cats

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

### Active substance:

Dexmedetomidine hydrochloride	0.5 mg
(equivalent to dexmedetomidine)	0.42 mg)

### Excipients:

Methyl parahydroxybenzoate (E 218)	1.6 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 case of known 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 insert 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: Cepedex is an  $\alpha_2$ -adrenoreceptor 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  $\alpha_2$ -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize dexmedetomidine-induced effects.

## 4.6 Adverse reactions (frequency and seriousness)

By virtue of its  $\alpha_2$ -adrenergic activity, dexmedetomidine causes a decrease in heart rate and body temperature.

In some dogs and cats, a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. 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 AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into 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, 1<sup>st</sup> and 2<sup>nd</sup> 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, 1<sup>st</sup> and 2<sup>nd</sup> degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3<sup>rd</sup> 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 (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1<sup>st</sup> degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2<sup>nd</sup> degree atrioventricular 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 used concurrently with 40 micrograms dexmedetomidine/ kg 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.

The stopper may be safely punctured up to 100 times.

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) 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 body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

<b>Dog Weight (kg)</b>	<b>Dexmedetomidine 125 micrograms/m<sup>2</sup></b>		<b>Dexmedetomidine 375 micrograms/m<sup>2</sup></b>		<b>Dexmedetomidine 500 micrograms/m<sup>2</sup>*</b>	
	<b>(mcg/kg)</b>	<b>(ml)</b>	<b>(mcg/kg)</b>	<b>(ml)</b>	<b>(mcg/kg)</b>	<b>(ml)</b>
2-3	9.4	0.04	28.1	0.12	40	0.15
3.1-4	8.3	0.05	25	0.17	35	0.2
4.1-5	7.7	0.07	23	0.2	30	0.3
5.1-10	6.5	0.1	19.6	0.29	25	0.4
10.1-13	5.6	0.13	16.8	0.38	23	0.5
13.1-15	5.2	0.15	15.7	0.44	21	0.6
15.1-20	4.9	0.17	14.6	0.51	20	0.7
20.1-25	4.5	0.2	13.4	0.6	18	0.8
25.1-30	4.2	0.23	12.6	0.69	17	0.9
30.1-33	4	0.25	12	0.75	16	1.0
33.1-37	3.9	0.27	11.6	0.81	15	1.1
37.1-45	3.7	0.3	11	0.9	14.5	1.2
45.1-50	3.5	0.33	10.5	0.99	14	1.3
50.1-55	3.4	0.35	10.1	1.06	13.5	1.4
55.1-60	3.3	0.38	9.8	1.13	13	1.5
60.1-65	3.2	0.4	9.5	1.19	12.8	1.6
65.1-70	3.1	0.42	9.3	1.26	12.5	1.7
70.1-80	3	0.45	9	1.35	12.3	1.8
>80	2.9	0.47	8.7	1.42	12	1.9

\*only IM

<b>For deep sedation and analgesia with butorphanol</b>		
<b>Dog Weight (kg)</b>	<b>Dexmedetomidine 300 micrograms/m<sup>2</sup> intramuscularly</b>	
	<b>(mcg/kg)</b>	<b>(ml)</b>
2-3	24	0.12
3.1-4	23	0.16
4.1-5	22.2	0.2
5.1-10	16.7	0.25
10.1-13	13	0.3
13.1-15	12.5	0.35
15.1-20	11.4	0.4
20.1-25	11.1	0.5
25.1-30	10	0.55
30.1-33	9.5	0.6
33.1-37	9.3	0.65
37.1-45	8.5	0.7
45.1-50	8.4	0.8
50.1-55	8.1	0.85
55.1-60	7.8	0.9
60.1-65	7.6	0.95
65.1-70	7.4	1

70.1-80	7.3	1.1
>80	7	1.2

#### Cats:

The dose for cats is 40 micrograms dexmedetomidine hydrochloride/kg bw equal to a dose volume of 0.08 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 Weight (kg)	Dexmedetomidine 40 micrograms/kg intramuscularly	
	(mcg/kg)	(ml)
1-2	40	0.1
2.1-3	40	0.2
3.1-4	40	0.3
4.1-6	40	0.4
6.1-7	40	0.5
7.1-8	40	0.6
8.1-10	40	0.7

#### 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)**

##### 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 meter body surface area). The dose volume of atipamezole at the concentration of 5 mg/ml equals the dose volume of Cepedex 0.5 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-half the volume of Cepedex 0.5 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, 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 stimulus.

Dexmedetomidine is a potent and selective  $\alpha_2$ -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  $\alpha_2$ -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 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. 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 coadministered 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 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 coadministered with other substances, which affect hepatic circulation.

## 6. PHARMACEUTICAL PARTICULARS



## **6.1 List of excipients**

Methyl parahydroxybenzoate (E 218)  
Propyl parahydroxybenzoate  
Sodium chloride  
Sodium hydroxide (E 524) (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: 3 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, 10 ml and 20 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

1 vial of 20 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(S)**

EU/2/16/200/004-007

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation:13/12/2016

<Date of last renewal:> <{DD/MM/YYYY}> <{DD month YYYY}.>

#### **10. DATE OF REVISION OF THE TEXT**

<{MM/YYYY}>

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

#### **PROHIBITION OF SALE, SUPPLY AND/OR USE**

Not applicable.

**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 WARNINGS, IF NECESSARY**

Read the package leaflet before use

**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)**

EU/2/16/200/001 (5 ml)

EU/2/16/200/002 (10 ml)

EU/2/16/200/003 (5 x 10 ml)

**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.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**

**Cardboard box (0.5 mg/ml)**

**1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Cepedex 0.5 mg/ml solution for injection for dogs and cats  
dexmedetomidine hydrochloride



**2. STATEMENT OF ACTIVE SUBSTANCES**

1 ml contains:

Dexmedetomidine hydrochloride	0.5 mg
(equivalent to dexmedetomidine	0.42 mg)

**3. PHARMACEUTICAL FORM**

Solution for injection

**4. PACKAGE SIZE**

5 ml  
10 ml  
5 x 10 ml  
20 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 WARNINGS, IF NECESSARY**

Read the package leaflet before use

**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 Handelsges. mbH  
Ostlandring 13, 31303 Burgdorf  
Deutschland

**16. MARKETING AUTHORISATION NUMBER(S)**

EU/2/16/200/004 (5 ml)  
EU/2/16/200/005 (10 ml)  
EU/2/16/200/006 (5 x 10 ml)  
EU/2/16/200/007 (20 ml)

**17. MANUFACTURER'S BATCH NUMBER**

Lot.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

Glass vials of 5, 10 or 20 ml (0.5 mg/ml)

**1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Cepedex 0.5 mg/ml injection  
dexmedetomidine hydrochloride



**2. QUANTITY OF THE ACTIVE SUBSTANCE(S)**

0.5 mg/ml

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

5 ml  
10 ml  
20 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 case of known hypersensitivity to the active substance or to any of the excipients.

**6. ADVERSE REACTIONS**

By virtue of its  $\alpha_2$ -adrenergic activity, dexmedetomidine causes a decrease in heart rate and body temperature.

In some dogs and cats, a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. 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 AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into 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, 1<sup>st</sup> and 2<sup>nd</sup> 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, 1<sup>st</sup> and 2<sup>nd</sup> degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3<sup>rd</sup> 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 (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1<sup>st</sup> degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2<sup>nd</sup> degree atrioventricular block, or escape beats/rhythms.

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

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).

## **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) 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 body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.



Dog Weight (kg)	Dexmedetomidine 125 micrograms/m <sup>2</sup>		Dexmedetomidine 375 micrograms/m <sup>2</sup>		Dexmedetomidine 500 micrograms/m <sup>2</sup> *	
	(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 Weight (kg)	Dexmedetomidine 300 micrograms/m <sup>2</sup> 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 weight 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 Weight (kg)	Dexmedetomidine 40 micrograms/kg intramuscularly	
	(mcg/kg)	(ml)
1-2	40	0.5
2.1-3	40	1

For higher weight 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 WARNINGS**

### Special warnings

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 insert 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: Cepedex is an  $\alpha_2$ -adrenoreceptor 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  $\alpha_2$ -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize 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 used concurrently with 40 micrograms dexmedetomidine/ kg 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 meter 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, 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**

### **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.

**PACKAGE LEAFLET**  
Cepedex 0.5 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 0.5 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	0.5 mg
(equivalent to dexmedetomidine)	0.42 mg)

**Excipient(s):**

Methyl parahydroxybenzoate (E 218)	1.6 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 case of known hypersensitivity to the active substance or to any of the excipients.

## **6. ADVERSE REACTIONS**

By virtue of its  $\alpha_2$ -adrenergic activity, dexmedetomidine causes a decrease in heart rate and body temperature.

In some dogs and cats, a decrease in respiratory rate may occur. Rare instances of pulmonary oedema have been reported. 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 AV-block or extrasystole. Expected respiratory events are bradypnoea, intermittent respiratory patterns, hypoventilation, and apnoea. In clinical trials the incidence of hypoxaemia was common, especially within the 15 first minutes into 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, 1<sup>st</sup> and 2<sup>nd</sup> 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, 1<sup>st</sup> and 2<sup>nd</sup> degree AV block and sinus arrest. Supraventricular and ventricular premature complexes, sinus pause and 3<sup>rd</sup> 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 (followed by ketamine or propofol) frequently resulted in sinus bradycardia and sinus arrhythmia, occasionally resulted in 1<sup>st</sup> degree atrioventricular block, and rarely resulted in supraventricular premature depolarizations, atrial bigeminy, sinus pauses, 2<sup>nd</sup> degree atrioventricular block, or escape beats/rhythms.

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

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).

## **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) 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 dosage 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 body weight are presented in the following tables. Use of an appropriately graduated syringe is recommended to ensure accurate dosing when administering small volumes.

Dog Weight (kg)	Dexmedetomidine 125 micrograms/m <sup>2</sup>		Dexmedetomidine 375 micrograms/m <sup>2</sup>		Dexmedetomidine 500 micrograms/m <sup>2</sup> *	
	(mcg/kg)	(ml)	(mcg/kg)	(ml)	(mcg/kg)	(ml)
2-3	9.4	0.04	28.1	0.12	40	0.15
3.1-4	8.3	0.05	25	0.17	35	0.2
4.1-5	7.7	0.07	23	0.2	30	0.3
5.1-10	6.5	0.1	19.6	0.29	25	0.4
10.1-13	5.6	0.13	16.8	0.38	23	0.5
13.1-15	5.2	0.15	15.7	0.44	21	0.6
15.1-20	4.9	0.17	14.6	0.51	20	0.7
20.1-25	4.5	0.2	13.4	0.6	18	0.8
25.1-30	4.2	0.23	12.6	0.69	17	0.9
30.1-33	4	0.25	12	0.75	16	1.0
33.1-37	3.9	0.27	11.6	0.81	15	1.1
37.1-45	3.7	0.3	11	0.9	14.5	1.2
45.1-50	3.5	0.33	10.5	0.99	14	1.3
50.1-55	3.4	0.35	10.1	1.06	13.5	1.4
55.1-60	3.3	0.38	9.8	1.13	13	1.5
60.1-65	3.2	0.4	9.5	1.19	12.8	1.6
65.1-70	3.1	0.42	9.3	1.26	12.5	1.7
70.1-80	3	0.45	9	1.35	12.3	1.8
>80	2.9	0.47	8.7	1.42	12	1.9

\*only intramuscularly

For deep sedation and analgesia with butorphanol		
Dog Weight (kg)	Dexmedetomidine 300 micrograms/m <sup>2</sup> intramuscularly	
	(mcg/kg)	(ml)
2-3	24	0.12
3.1-4	23	0.16
4.1-5	22.2	0.2
5.1-10	16.7	0.25
10.1-13	13	0.3
13.1-15	12.5	0.35
15.1-20	11.4	0.4
20.1-25	11.1	0.5
25.1-30	10	0.55
30.1-33	9.5	0.6
33.1-37	9.3	0.65
37.1-45	8.5	0.7
45.1-50	8.4	0.8
50.1-55	8.1	0.85
55.1-60	7.8	0.9
60.1-65	7.6	0.95
65.1-70	7.4	1
70.1-80	7.3	1.1
>80	7	1.2



### Cats:

The dose for cats is 40 micrograms dexmedetomidine hydrochloride/kg bw equal to a dose volume of 0.08 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 Weight (kg)	Dexmedetomidine 40 micrograms/kg intramuscularly	
	(mcg/kg)	(ml)
1-2	40	0.1
2.1-3	40	0.2
3.1-4	40	0.3
4.1-6	40	0.4
6.1-7	40	0.5
7.1-8	40	0.6
8.1-10	40	0.7

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

The stopper may be safely punctured up to 100 times.

## **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 WARNINGS**

### Special warnings

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 insert 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 product with caution.

Advice to physicians: Cepedex is an  $\alpha_2$ -adrenoreceptor 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  $\alpha_2$ -adrenoceptor antagonist, atipamezole, which is approved for use in animals, has been used in humans only experimentally to antagonize 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 used concurrently with 40 micrograms dexmedetomidine/ kg 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 meter body surface area). The dose volume of atipamezole at the concentration of 5 mg/ml equals the dose volume of Cepedex 0.5 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-half (1/2) the volume of Cepedex 0.5 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, 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**

### **15. OTHER INFORMATION**

Colourless Type I glass vials of 5 ml, 10 ml and 20 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  
1 vial of 20 ml

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

**België/Belgique/Belgien**

CP-Pharma Handelsgesellschaft mbH  
Ostlandring 13  
D-31303 Burgdorf  
Allemagne

**Република България**

CP-Pharma Handelsgesellschaft mbH  
Ostlandring 13  
D-31303 Burgdorf  
Германия

**Česká republika**

CP-Pharma Handelsgesellschaft mbH  
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D-31303 Burgdorf  
Německo

**Danmark**

ScanVet Animal Health A/S  
Kongevejen 66  
DK-3480 Fredensborg  
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Danmark

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**Eesti**

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**Ελλάδα**

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Γερμανία

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Vokietija

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Alemanha

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