

**IRISH MEDICINES BOARD ACT 1995**

**EUROPEAN COMMUNITIES (ANIMAL REMEDIES) REGULATIONS 2007**

**(S.I. No. 144 of 2007)**

VPA: **10989/050/001**

Case No: 7003128

The Irish Medicines Board in exercise of the powers conferred on it by Animal Remedies Regulations (S.I. No. 144 of 2007) hereby grants to:

**Eurovet Animal Health B.V.**

**Handelsweg 25, 5531 AE Bladel, Netherlands**

an authorisation, subject to the provisions of the said Regulations and the general conditions of the attached authorisation, in respect of the Veterinary Medicinal Product:

**Sedaxylan 20 mg/ml Solution for injection**

The particulars of which are set out in Part 1 and Part 2 of the said Schedule. The authorisation is also subject to any special conditions as may be specified in the said Schedule.

The authorisation, unless previously revoked, shall continue in force from **02/05/2008**.

Signed on behalf of the Irish Medicines Board

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A person authorised in that behalf by the said Board.

(NOTE: From this date of effect, this authorisation replaces any previous authorisation in respect of this product which is now null and void.)

Part II

Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Sedaxylan, 20 mg/ml  
Solution for injection for dogs, cats, horses and cattle.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Xylazine (base)	20.0	mg
Equivalent to 23.32 mg xylazine hydrochloride		

Excipients:	Function	Amount
Methyl parahydroxybenzoate (E 218)	preservative	1.0 mg
Propyl parahydroxybenzoate (E 216)	preservative	0.1 mg
Propylene glycol	Co solvent	8.9 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection  
Clear and colourless.

4 CLINICAL PARTICULARS

4.1 Target Species

Dogs, cats, horses and cattle.

4.2 Indications for use, specifying the target species

Sedation of dogs, cats, horses and cattle.

4.3 Contraindications

Do not use in the later stages of pregnancy, see section 4.7  
Do not use in animals with oesophageal obstruction, and torsion of the stomach, as the muscle relaxant properties of the drug appear to accentuate the effects of the obstruction and, because of possible vomiting.  
Do not use in animals with renal or hepatic impairment, respiratory dysfunction, cardiac abnormalities, hypotension and/or shock. Do not use in diabetic animals.  
Do not use in calves younger than 1 week of age, foals younger than 2 weeks or in puppies and kittens younger than 6 weeks. See also section 4.7.

## 4.4 Special warnings for each target species

### Horses:

- Xylazine inhibits the normal intestinal motility. Therefore, it should only be used in horses with colic, that are not responsive to analgesics. The use of xylazine should be avoided in horses with caecal malfunction.
- After treatment of horses with xylazine, the animals are reluctant to walk, so whenever possible the drug should be administered in the place where the treatment/investigation is going to take place.
- Caution should be taken in the administration of the product to horses susceptible to laminitis.
- Horses with air way disease or malfunction may develop life-threatening dyspnoea.
- The dose should be kept as low as possible.

### Cats and dogs:

- Xylazine inhibits the normal intestinal motility. This may make xylazine sedation undesirable for upper gastro-intestinal radiographs, because it promotes filling of the stomach with gas and makes interpretation less certain.
- Brachycephalic dogs with air way disease or malfunction may develop life-threatening dyspnoea.

### Cattle:

- Ruminants are highly susceptible to the effects of xylazine. Normally cattle remain standing at the lower doses, but some animals may lie down. At the highest recommended doses most animals will lie down and some animals may relapse in lateral recumbency.
- Reticulo-ruminal motor functions are depressed after injection of xylazine. This may result in bloat. It is advisable to withhold feed and water for several hours before administration of xylazine.
- In cattle the ability to eructate, cough and swallow is retained but reduced during the period of sedation, therefore cattle must be closely watched during the recovery period: the animals should be maintained in sternal recumbency.
- In cattle life threatening effects may occur after intramuscular doses above 0.5 mg/kg body weight (respiratory and circulatory failure). Therefore very precise dosing is required.

## 4.5 Special precautions for use

### **Special precautions for use in animals:**

- Older and exhausted animals are more sensitive to xylazine, whilst nervous or highly excitable animals may require a relatively high dose.
- In case of dehydration, xylazine should be used cautiously.
- Emesis is generally seen within 3-5 minutes after xylazine administration in cats and dogs. It is advisable to fast dogs and cats for 12 hours prior to surgery; they may have free access to drinking water.
- Do not exceed the recommended dosage.
- Following administration animals should be allowed to rest quietly until the full effect has been reached.
- It is advised to cool animals when the ambient temperature is above 25°C and to keep animals warm at low temperatures.
- Because the analgesic properties of xylazine are insufficient, in painful procedures xylazine should always be used in combination with a local or general analgesic.
- Xylazine produces a certain degree of ataxia; therefore, xylazine must be used cautiously in procedures involving the distal extremities and in standing castrations in the horse.
- Treated animals should be monitored until the effect has faded totally (e.g. cardiac and respiratory function, also in the post-operative phase).
- For use in young animals, see the age restriction mentioned in 4.3. If the product is intended to be used in young animals below these age-limits, a benefit/risk assessment should be made by the veterinarian.

### **Special precautions to be taken by the person administering the veterinary medicinal product to animals:**

- In the 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.
- Irritation, sensitisation, contact dermatitis and systemic effects cannot be excluded after skin contact.
- Avoid skin contact and wear impermeable gloves when handling the product.
- Wash the exposed skin immediately after exposure with large amounts of water.
- In the case of accidental projection of the product into the eyes, rinse abundantly with fresh water. If irritation persists, seek the advice of a physician.
- Remove contaminated clothes.
- Pregnant women should not handle the product.
- **ADVICE TO DOCTORS:** Xylazine is an  $\alpha$ -adrenoreceptor agonist whose toxicity may cause clinical effects including sedation, respiratory depression and coma, bradycardia and hypotension and hyperglycaemia. Ventricular arrhythmias have also been reported. Treatment should be supportive with appropriate intensive therapy.

## 4.6 Adverse reactions (frequency and seriousness)

In general, side effects, typical for an  $\alpha$ 2-adrenergic agonist, like bradycardia, reversible arrhythmia and hypotension can occur. Thermoregulation can be influenced and consequently body temperature can decrease or increase dependant on the ambient temperature. Depression of respiration and / or respiratory arrest can occur, especially in cats.

### Cats and dogs

- Cats and dogs frequently vomit during the onset of the xylazine-induced sedation, especially when the animals have just been fed.
- Animals may show profound salivation following an injection with xylazine.
- Other adverse effects for dogs and cats include: muscle tremors, bradycardia with AV-block, hypotension, reduced respiratory rate, movement in response to strong auditory stimuli, and increased urination in cats.
- In cats xylazine causes uterine contractions and it may induce premature parturition.
- In dogs, adverse effects are generally more pronounced after subcutaneous administration compared to intramuscular and the effect (efficacy) can be less predictable.

### Cattle

- In cattle xylazine may induce premature parturition, and it also reduces implantation of the ovum.
- Cattle, which have received high doses of xylazine sometimes suffer from loose faeces for 24 hours afterwards.
- Other adverse reactions include profound salivation, ruminal atony, atony of the tongue, regurgitation, bloating, hypothermia, bradycardia, increased urination and reversible prolapse of the penis.
- In cattle, adverse effects are generally more pronounced after intramuscular administration compared to intravenous.

### Horses

- Horses often sweat as the effects of the sedation are wearing off.
- Severe bradycardia and reduced respiratory rate have been reported especially in horses.
- More frequent urination has been reported.
- Muscle tremors and movement in response to sharp auditory or physical stimuli are possible. Although rare, violent reactions have been reported in horses following the administration of xylazine.
- Ataxia and reversible prolapse of the penis may occur.
- In very rare cases xylazine may induce mild colic as the gut motility is depressed temporarily. As a preventive measure the horse should receive no feed after sedation until the effect has faded completely.

## 4.7 Use during pregnancy, lactation or lay

Although laboratory studies in rats have not shown any evidence of teratogenic or foetotoxic effects the use of the product during the first two trimesters of pregnancy should only be made according to the benefit/risk assessment by the responsible veterinarian.

Do not use in the later stages of pregnancy (particularly in cattle and cats), because xylazine causes uterine contractions and it may induce premature labour.

Do not use in cattle receiving ovum transplants as the increased uterine tone may reduce the chance of implantation of the ovum.

## 4.8 Interaction with other medicinal products and other forms of interaction

Other CNS depressant agents (barbiturates, narcotics, anaesthetics, tranquillizers, etc.) may cause additive CNS depression if used with xylazine. Dosages of these agents may need to be reduced. Xylazine should therefore be used cautiously in combination with neuroleptics or tranquillizers.

Xylazine should not be used in combination with sympathomimetic drugs such as epinephrine as ventricular arrhythmia may follow.

## 4.9 Amounts to be administered and administration route

This product is intended for single intravenous, intramuscular or subcutaneous injection dependent upon the species in which it is to be used. The individual response to xylazine is somewhat varied (as with other sedatives), and depends partly on the dosage, the age of the patient, temperament of the patient, the surroundings (stress) and general condition (diseases, fat percentage, etc.). Doses also depend on the desired degree of sedation. Generally time to onset of sedation and recovery will take longer after intramuscular or subcutaneous injection at the recommended dosages than after intravenous injection. First effects are usually seen within 2 minutes following intravenous injection and within 5 to 10 minutes after intramuscular or subcutaneous injection. The maximum effect is seen 10 minutes later. It is generally seen that an increase in dose will lead to an increase in the level of sedation, until a maximum level is attained. Increasing the dosage beyond this point will lead to increase of the duration of the sedation. Recovery in calves may be prolonged after administration of 1.5 x the recommended dose. If the required depth of sedation is not achieved it is unlikely that repetition of the dose will prove more effective. In that case it is advisable to allow complete recovery, repeating the procedure with a higher dose after 24 hours.

Accurately ascertain the body weight of an animal before treatment with xylazine. Use a syringe with appropriate gradations.

Dogs:	1.0 - 2.0	mg per kg body weight intramuscularly or subcutaneously
	0.5 – 1.0	<i>ml injection solution/10 kg body weight IM or SC</i>
	0.7 - 1.0	mg per kg body weight intravenously.
	0.35 – 0.5	<i>ml injection solution/10 kg body weight IV</i>
Cats:	0.5 - 1.0	mg per kg body weight intramuscularly or subcutaneously.
	0.125 – 0.25	<i>ml injection solution/ 5 kg body weight IM or SC</i>
Horses:	0.5 - 1.0	mg per kg body weight intravenously.
	2.5 – 5.0	<i>ml injection solution/100 kg body weight IV</i>
Cattle:	0.05 – 0.20	mg per kg body weight intramuscularly or
	0.25 – 1.0	<i>ml injection solution/100 kg body weight IM</i>
	0.03 – 0.10	mg per kg body weight intravenously.
	0.15 – 0.5	<i>ml injection solution/100 kg body weight IV</i>

The intravenous injection should be given slowly, especially in horses.

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

In the event of an accidental overdose, cardiac arrhythmias, hypotension, and profound CNS and respiratory depression may occur. Seizures have also been reported after an overdose. Xylazine can be antagonized by  $\alpha_2$ -adrenergic antagonists: atipamezole has been found to be a useful antidote in some cases. The recommended dosage is: 0.2 mg/kg for dogs and cats, 0.15 mg/kg for horses and 0.03 mg/kg for cattle.

To treat the respiratory depressant effects of xylazine, mechanical respiratory support with or without respiratory stimulants (e.g. doxapram) can be recommended.

## 4.11 Withdrawal Period(s)

- Horse (meat) - One day.
- Cattle (meat) - One day.
- Cattle (milk) - Zero days.

## 5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacologically xylazine hydrochloride is classified as a sedative and skeletal muscle relaxant.

ATC Vet Code : QN05C M92

Xylazine belongs to the  $\alpha_2$ -adrenoceptor agonists.

Xylazine is a  $\alpha_2$ -adrenoceptor agonist, that acts by stimulation of central and peripheral  $\alpha_2$ -adrenoceptors. Through its central stimulation of  $\alpha_2$ -adrenoceptors, xylazine has potent antinociceptive activity. In addition  $\alpha_2$ -adrenergic activity, xylazine has  $\alpha_1$ -adrenergic effects. Xylazine also produces skeletal muscle relaxation by inhibition of intraneuronal transmission of impulses at the central level of the central nervous system. The analgesic and skeletal muscle relaxation properties of xylazine show considerable interspecies variations. Sufficient analgesia generally will be attained in combination with other products only.

In many species, administration of xylazine produces a short-lived arterial pressor effect followed by a longer period of hypotension and bradycardia. These contrasting actions upon the arterial pressure apparently are related to the  $\alpha_2$ - and  $\alpha_1$ -adrenergic actions of xylazine.

Xylazine has several endocrine effects. Insulin (mediated by  $\alpha_2$ -receptors in pancreatic  $\beta$ -cells which inhibit insulin release), ADH (decreased production of ADH, causing polyuria) and FSH (decreased) are reported to be influenced by xylazine.

### 5.2 Pharmacokinetic properties

Absorption (and action) is rapid following intramuscular injection. Levels of drug peak rapidly (usually within 15 minutes) and then decline exponentially. Xylazine is a highly lipid soluble organic base and diffuses extensively and rapidly ( $V_d$  1.9-2.7). Within minutes after an intravenous injection, it can be found in a high concentration in the kidneys, the liver, the CNS, the hypophyses, and the diaphragm. So there is a very rapid transfer from the blood vessels to the tissues. Intramuscular bioavailability is incomplete and variable ranging from 52-90% in the dog to 40-48% in the horse. Xylazine is metabolised extensively and eliminated rapidly ( $\pm 70\%$  via the urine, while the enteric elimination is  $\pm 30\%$ ). The rapid elimination of xylazine is probably related to an extensive metabolism rather than to a rapid renal excretion of unchanged xylazine.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Citric acid monohydrate,  
Sodium citrate,  
Methyl parahydroxybenzoate (E 218),  
Propyl parahydroxybenzoate (E 216),  
Propylene glycol,  
Water for Injections

### 6.2 Incompatibilities

Sedaxylan should not be mixed with other medicinal products.

### **6.3 Shelf-life**

Shelf-life of the veterinary medicinal product as packaged for sale: 36 months

Shelf-life after first opening the container: 28 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**

- Vial
  - \* volume 30 ml and 50 ml
  - \* contents 25 ml and 50 ml
  - \* glass type II
  - \* amber coloured
- Stopper
  - \* bromobutyl rubber stopper type I
  - \* secured with aluminium cap

Not all pack sizes may be marketed.

### **6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials**

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

## **7 MARKETING AUTHORISATION HOLDER**

Eurovet Animal Health B.V.,  
Handelsweg 25, PO Box 179,  
5530 AD Bladel,  
The Netherlands.

## **8 MARKETING AUTHORISATION NUMBER(S)**

VPA 10989/50/1

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

2<sup>nd</sup> May 2003

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

19<sup>th</sup> October 2007