PACKAGE LEAFLET

Pronestesic 40 mg/ml / 0.036 mg/ml solution for injection for horses, cattle, pigs and sheep (AT, BE, CY, CZ, DE, DK, EE, EL, ES, HR, IE, IT, LT, LU, LV, NL, PL, PT, SI, SK, UK)
Pronestesic vet 40 mg/ml / 0.036 mg/ml solution for injection for horses, cattle, pigs and sheep (FI, IS, SE)
Malleva vet 40 mg/ml / 0.036 mg/ml solution for injection for horses, cattle, pigs and sheep (NO)
Pronestesic 34.65 mg/ml / 0.02 mg/ml solution for injection for horses, cattle, pigs and sheep (FR)

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

FATRO S.p.A. - Via Emilia, 285 - Ozzano Emilia (Bologna), Italy.

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Pronestesic 40 mg/ml / 0.036 mg/ml solution for injection for horses, cattle, pigs and sheep (AT, BE, CY, CZ, DE, DK, EE, EL,ES, HR, IE, IT, LT, LU, LV, NL, PL, PT, SI, SK, UK)
Pronestesic vet 40 mg/ml / 0.036 mg/ml solution for injection for horses, cattle, pigs and sheep (FI, IS, SE)
Malleva vet 40 mg/ml / 0.036 mg/ml solution for injection for horses, cattle, pigs and sheep (NO)
Pronestesic 34.65 mg/ml / 0.02 mg/ml solution for injection for horses, cattle, pigs and sheep (FR)
procaine hydrochloride/epinephrine tartrate

3. STATEMENT OF THE ACTIVE SUBSTANCES AND OTHER INGREDIENTS (AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, HR, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, SK, UK)

1 ml contains:
Active substances: procaine hydrochloride 40 mg (equivalent to 34.65 mg procaine) - epinephrine tartrate 0.036 mg (equivalent to 0.02 mg epinephrine); **Excipients:** sodium metabisulfite (E223) - sodium methyl parahydroxybenzoate (E219) - disodium edetate.

3. STATEMENT OF THE ACTIVE SUBSTANCES AND OTHER INGREDIENTS (FR)

1 ml contains:
Active substances: procaine (as hydrochloride) 34.65 mg (equivalent to 40 mg procaine hydrochloride) - epinephrine (as tartrate) 0.02 mg (equivalent to 0.036 mg epinephrine tartrate); **Excipients:** sodium metabisulfite (E223) - sodium methyl parahydroxybenzoate (E219) - disodium edetate

Clear colourless solution, free of visible particles.

4. INDICATIONS

Local anaesthesia with a long-lasting anaesthetic effect.

Horses, cattle, pigs and sheep: infiltration anaesthesia and perineural anaesthesia (see section 12).

5. CONTRAINDICATIONS

Do not use in animals in a state of shock.
Do not use in animals with cardiovascular problems.
Do not use in animals treated with sulphonamides.
Do not use in animals treated with phenothiazine (see section 12).
Do not use with cyclopropane- or halothane-based anaesthetics (see section 12).
Do not use to anaesthetise regions with terminal circulation (ears, tail, penis, etc.), owing to the risk of tissue necrosis following complete circulatory arrest, due to the presence of epinephrine (substance with a vasoconstrictor action).
Do not use in case of hypersensitivity to the active substance or to any of the excipients.
Do not administer by the intravenous or the intra-articular route.
Do not use in case of hypersensitivity to local anaesthetics belonging to the esters subgroup or in case of possible allergic cross reactions to p-aminobenzoic acid and sulphonamides.

6. ADVERSE REACTIONS

The procaine may cause hypotension.
In a few cases, particularly in horses, phenomena of excitability to the CNS may be observed (agitation, tremors, convulsions) following the administration of procaine.
Allergic reactions to procaine are quite common; only in rare cases anaphylactic reactions have been observed.
A hypersensitivity to local anaesthetics belonging to the esters subgroup is known.
In exceptional cases tachycardia may occur (epinephrine). In case of inadvertent intravascular injection toxic reactions frequently appear. These manifest in an excitation of the central nervous system (restlessness, tremors, convulsions), followed by depression; death is the result of respiratory paralysis. In case of CNS excitation short acting barbiturates should be administered, as well as products for acidification of urine, so as to support renal excretion. In case of allergic reactions, antihistamines or corticoids can be given. Allergic shock is treated with epinephrine.
If you notice any serious effect or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Horses, cattle, pigs and sheep.

8. DOSAGE FOR EACH SPECIES, ROUTES AND METHOD OF ADMINISTRATION

- For subcutaneous and perineural use.
- For onset and duration of effect, please see section 15.

1. <u>Local anaesthesia or by infiltration: inject into the subcutis or around the area involved</u>

   Horses, cattle, pigs and sheep: 2.5-10 ml of the product/animal (corresponding to100-400 mg of Procaine hydrochloride + 0.09-0.36 mg of Epinephrine tartrate)

2. <u>Perineural anaesthesia: inject close to the branch of the nerve</u>

Horses, cattle, pigs and sheep: 5-10 ml of the product/animal (corresponding to 200-400 mg of Procaine hydrochloride + 0.18-0.36 mg of Epinephrine tartrate).

For lower limb blocks in horses, the dose should be divided between two or more injection sites depending on the dose. See also section 12.

The vial may be broached up to 20 times.

9. ADVICE ON CORRECT ADMINISTRATION

Do not administer by the intra-articular route.
To avoid inadvertent intravenous administration, draw back the plunger of the syringe to check for the absence of blood before injecting.
The vial may be broached up to 20 times.

10. WITHDRAWAL PERIOD

Withdrawal period:

Horses, cattle and sheep:
Meat and offal: zero days
Milk: zero hours
Pigs:
Meat and offal: zero days

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.
Do not use this veterinary medicinal product after the expiry date which is stated on the vial and carton label after "EXP". The expiry date refers to the last day of that month.
Shelf-life after first opening the vial: 28 days.

When the container is opened for the first time, the date on which any product remaining in the container should be discarded, should be worked out using the in-use shelf-life which is specified on this package leaflet. This discard date should be written in the space provided on the label.

12. SPECIAL WARNINGS

Special warnings for each target species

None

Special precautions for use in animals
To avoid inadvertent intravenous administration, draw back the plunger of the syringe to check for the absence of blood before injecting.
Due to local tissue damage, wounds or abscesses may be difficult to anaesthetise using local anaesthetics.

Perform local anaesthesia at ambient temperature. At higher temperatures, the risk of toxic reactions is higher owing to the greater absorption of procaine.
As with other local anaesthetics containing procaine, the product should be used with caution in animals with epilepsy or with changes in respiratory or renal function.
When injected near to wound edges, the product may lead to necrosis along the edges.
The product should be used with caution in lower limb blocks due to the risk of digital ischaemia.
Use with caution in horses due to risk of coat colour at the site of injection turning permanently white.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Avoid direct contact of the skin with the veterinary medicinal product. In case of spillage onto skin or eyes, rinse immediately with plenty of water. If irritation occurs, seek medical advice immediately and show the package leaflet or label to the physician.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or label to the physician.
People with known hypersensitivity to procaine or epinephrine must avoid contact with the veterinary medicinal product.

Use during pregnancy and lactation
Procaine crosses the placental barrier and is excreted in milk. Use only according to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction
Procaine inhibits the action of the sulphonamides owing to biotransformation to p-aminobenzoic acid, a sulphonamide antagonist.
Procaine prolongs the action of myorelaxants.
Procaine potentiates the action of antiarrhythmics e.g. procainamide.
Epinephrine potentiates the action of analgesic anaesthetics on the heart.

Do not use with cyclopropane- or halothane-based anaesthetics, as they increase cardiac sensitivity to epinephrine (a sympathomimetic) and may cause arrhythmia.
Due to these interactions, the veterinarian may adjust the dosage and should carefully monitor the effects on the animal.

Overdose (symptoms, emergency procedures, antidotes):
Symptoms related to overdose correlate with symptoms occurring after inadvertent intravascular injection as described in section 6.

Incompatibilities
In the absence of compatibility studies this veterinary medicinal product must not be mixed with other veterinary medicinal products.
The solution is incompatible with alkaline products, tannic acid or metal ions.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

[To be completed nationally]

15. OTHER INFORMATION

Pharmacodynamic properties

Procaine

Procaine is a synthetic local anaesthetic belonging to the esters group.
It is an ester of p-aminobenzoic acid, which is considered the lipophilic part of this molecule. Procaine has a stabilising effect on the membrane, that is, it reduces the permeability of the membrane of nerve cells, preventing the diffusion of sodium and potassium ions. In this way, there is no action potential and the conduction of excitability is inhibited. This inhibition leads to a local anaesthesia which is reversible. Nerve fibres show different sensitivity to local anaesthetics, which is determined by the thickness of the myelin sheath: fibres which are not surrounded by the myelin sheath are the most sensitive and fibres with a thin layer of myelin are anaesthetised more rapidly than those surrounded by a thicker myelin sheath.
Procaine has a latency period from 5 to 10 minutes after subcutaneous administration. Procaine has a short duration of action (maximum 30 - 60 minutes); with the addition of epinephrine to the solution, the duration of action is prolonged up to 45 - 90 minutes. The speed at which the anaesthesia is obtained depends on the animal species and age.
In addition to its local anaesthetic properties, procaine also has a vasodilator and antihypertensive action.

Epinephrine

Epinephrine is a catecholamine with sympathomimetic properties. It causes a local vasoconstriction which, slowing down absorption of procaine hydrochloride, prolongs the anaesthetic effect of procaine. The slow reabsorption of procaine decreases the risk of systemic toxic effects. Epinephrine also has a stimulant action on the myocardium.

Pharmacokinetic particulars

Procaine

After parenteral administration, procaine is rapidly reabsorbed in the blood, particularly owing to its vasodilatory properties. The absorption also depends on the degree of vascularisation of the injection site. The duration of action is relatively short, owing to rapid hydrolysis by serum cholinesterase. The addition of epinephrine, which has a vasoconstrictor action, slows down absorption, prolonging the local anaesthetic effect.
Binding to proteins is negligible (2%).
Procaine does not easily penetrate the tissues, owing to its poor liposolubility. However, it penetrates the central nervous system and the foetal plasma.
Procaine is rapidly and almost entirely hydrolysed to p-aminobenzoic acid and diethylaminoethanol by non-specific pseudocholinesterases, principally present in the plasma but also in the microsomes of the liver and other tissues. P-aminobenzoic acid, which inhibits the action of sulphonamides, is conjugated in its turn, for example with glucuronic acid, and excreted renally. Diethylaminoethanol, which is an active metabolite, decomposes in the liver. The metabolism of procaine differs from one animal species to the other.

The plasma half-life of procaine is short (60 - 90 minutes). It is rapidly and totally excreted renally in the form of metabolites. Renal clearance depends on the pH of the urine: in the case of an acid pH, renal excretion is higher; if the pH is alkaline, elimination is slower.

Epinephrine

After parenteral administration, epinephrine is well absorbed, but slowly, owing to the vasoconstriction induced by the substance itself. It can only be found in small quantities in the blood, because it has already been reabsorbed by the tissues.

Epinephrine and its metabolites distribute rapidly to the different organs.

Epinephrine is transformed into inactive metabolites in the tissues and in the liver by monoamine oxidase (MAO) enzymes and catechol-O-methyltransferase (COMT).

The systemic activity of epinephrine is short, owing to the rapidity of its excretion, which takes place largely by the renal route in the form of inactive metabolites.

Pack sizes:

1 x 50 ml
1 x 100 ml
1 x 250 ml
10 x 100 ml

Not all pack sizes may be marketed.