PARTICULARS TO APPEAR ON THE OUTER PACKAGE (Box containing 1 vial)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

EQUIDRONATE 500 mg, lyophilisate for solution for infusion

Tiludronic acid

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Lyophilisate for solution for infusion

3. PHARMACEUTICAL FORM

1 vial.

4. PACKAGE SIZE

5. TARGET SPECIES

Horses.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion.Read the package leaflet before use and disposal.

8. WITHDRAWAL PERIOD

Meat and offal: zero days

Not permitted for use in lactating animals producing milk for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

After reconstitution, the product may be stored at 2 - 8˚C for no longer than 24 hours.

10. EXPIRY DATE

EXP:

11. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

12. SPECIFIC PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

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

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IF APPLICABLE *[Distribution category]*

For animal treatment only.

POM-V

To be supplied only on veterinary prescription.

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

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Audevard

37-39 rue de Neuilly

92110 Clichy (France)

16. MARKETING AUTHORISATION NUMBER(S)

Vm 44684/4000

17. MANUFACTURER'S BATCH NUMBER

Lot:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS (Label)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

EQUIDRONATE 500 mg, lyophilisate for solution for infusion

Tiludronic acid

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Tiludronic acid 500mg as disodium salt.

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

4. ROUTE(S) OF ADMINISTRATION

For intravenous infusion.

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot:

7. EXPIRY DATE

Exp:

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

POM-V To be supplied only on veterinary prescription

[Include information under these headings as it appears in the SPC]

PACKAGE LEAFLET FOR:

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

Marketing authorisation holder:

Audevard

37-39 rue de Neuilly

92110 Clichy (France)

Manufacturer for the batch release:

Ceva Santé Animale, 10 av. de La Ballastière, 33500 Libourne, France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

EQUIDRONATE 500 mg, lyophilisate for solution for infusion

Tiludronic acid

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

Tiludronic acid (as disodium salt).....500 mg

4. INDICATION(S)

In horses as an aid in the treatment of clinical signs of lameness associated with bone spavin in combination with a controlled exercise regime.

5. CONTRAINDICATIONS

In the absence of any data relating to the adverse effects of tiludronic acid on the skeleton of young animals, do not administer to a horse less than 3 years old.
Do not administer to a horse with known impaired renal function. Renal function should ideally be evaluated prior to treatment.

Do not use in case of known hypersensitivity to biphosphonates or to any of the excipients.
See section on special warnings.

6. ADVERSE REACTIONS

The main adverse reactions related to treatment with tiludronic acid are signs of discomfort or signs of colic (expressed as belly watching, yawning, pawing or kicking, stretching, light bruxism, often combined with restlessness), softening of feaces and sweating. These side effects were observed in less than 15% of horses treated with the recommended therapeutic scheme.

The signs of colic appear within a few hours following treatment, are mild and transient and generally resolve spontaneously without requiring any specific treatment. In case signs persist, a non steroidal anti-inflammatory treatment or a spasmolytic treatment should be administered. The administration of an alpha 2 adrenergic agonist prior infusion may reduce the occurance of signs of colic.

As recumbency can be experienced post infusion, be aware that the horse should be free to lie down in a comfortable unrestricted area.

An increase in frequency of signs of discomfort and restlessness is observed when the infusion duration is less than 15 minutes.

On very rare occasions (less than 1 out of 20,000 horses) allergic or anaphylactic like reactions have been reported in treated horses: signs of reaction ranged from urticaria to anaphylactic shock which can be fatal. In rare cases, acute renal failure may occur within 1 week after administration of the product. Renal parameters should be monitored before administration of the product and water consumption and urine output should be monitored where possible after administration.If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Horses over 3 years of age.

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

1 mg of tiludronic acid per kg of body weight, corresponding to 5 ml of reconstituted solution per 100 kg, by intravenous route, by infusion.

The method of administration below should be followed:

- Using a sterile needle and a suitable sterile disposable syringe, remove 25 ml of 0.9% Sodium Chloride solution or 5% Glucose solution from a 1 l to 3 l infusion container.
- Add the 25 ml of isotonic Sodium Chloride or Glucose solution to the vial of powder.
- Shake until the powder is completely dissolved.
- Adhering to strict aseptic technique, inject the reconstituted solution into the infusion container
- Gently invert the container several times.
- Administer through a suitable needle or catheter inserted into the jugular vein and connected to the infusion container with sterile disposable infusion tubing.

The product should be infused over 30 minutes at an even rate. Fluctuations in the infusion rate could increase the risk of the horse showing signs of colic during or after the infusion.

Do not exceed the infusion rate as this could increase the risk of the horse showing signs of colic during or after infusion.

Do not exceed the recommended dosage.

9. ADVICE ON CORRECT ADMINISTRATION

10. WITHDRAWAL PERIOD(S)

Meat and offal: zero days

Not permitted for use in lactating animals producing milk for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.

Keep the vial in the outer carton in order to protect from light.
Do not use after the expiry date stated on the carton and label after EXP.

Shelf-life after reconstitution according to directions: 24 hours at 2 to 8ºC.

12. SPECIAL WARNING(S)

Special precautions for use in animals

The clinical effect of the product depends on the presence of osteolytic processes causing pain and leading to lameness. The product should be used only after a proper diagnosis combining a complete orthopaedic clinical examination including local analgesia and appropriate imaging techniques in order to identify the cause of pain and the nature of bone lesions.

It is recommended to respect the recommended 30 minute duration of infusion as the duration of infusion has an effect on the occurrence or severity of the adverse reactions. (increase in frequency of signs of discomfort and restlessness observed when the infusion duration is less than 15 minutes).

It is advisable for an experienced horse person to observe the horse for the first four hours following the infusion due to the possible onset of side effects.

The product should be administered with caution in a hypocalcemic horse. In this case, it is advised to slow down the rate of the infusion. As the risk of side effects might be increased under these circumstances, these animals should be the subject of particularly close surveillance.

Because of its mild hypocalcemic effect, the product should be administered with caution in horse with disorders of heart function. In this case, it is advisable to slow down the rate of infusion.

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

Avoid contact with skin and eyes.

Avoid accidental self-injection: it is recommended to insert the intravenous infusion needle into the vein before the reservoir containing the product is connected.

In the case of self injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Wear impervious gloves when preparing the solution for injection

Wash hands after use.

Pregnancy and Lactation

Studies conducted on laboratory animals (mice, rats, rabbits) did not reveal any embryotoxic, foetotoxic or teratogenic effects nor effects on peri- or post-natal development. Particularly, no adverse effects have been observed on the skeleton.

The safety of the product has not been studied in pregnant or lactating mares. The use of the product during pregnancy or lactation in mares is not recommended.

Interactions

Do not mix or concomitantly administer intravenously the reconstituted solution with solutions containing divalent metal ions (Ca2+ or Mg2+) such as Lactated Ringers. A solution of tiludronic acid may form complexes with these ions.
Avoid concomitant intravenous administration with drugs that can reduce serum calcium (such as tetracyclines) or whose toxicity can be exacerbated by a reduction in serum calcium (such as aminoglycosides).

In a field trial, the co-administration of the product with NSAIDs, spasmolytics or alpha 2 adrenergic agonists was well tolerated.

Regarding other medicinal products, no data are available.

In the absence of compatability studies, this veterinary medicinal product must not be mixed with other veterinary medicinal product.

Overdose

At 2, 3 or 5 times the recommended dosage, an increase in frequency of the side effects, in particular restlessness, signs of discomfort or signs of colic, is observed.

These signs may appear during or after the infusion, are usually mild and transient and generally resolve spontaneously at the end of the infusion without requiring any specific treatment. In cases where signs persist, conventional treatments should be administered.

Incompatibilities

Do not mix or concomitantly administer intravenously the reconstituted solution with solutions containing divalent metal ions (Ca2+ or Mg2+) such as Lactated Ringers. A solution of tiludronic acid may form complexes with these ions. In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal product.

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 product should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

March 2022

15. OTHER INFORMATION>

Pharmacodynamic properties

The pharmacodynamic effects of tiludronic acid have been investigated *in-vitro*, in laboratory animals and in the horse.

Tiludronic acid exerts its inhibitory effect on bone resorption by blocking some of the osteoclast metabolic pathways (production of non-hydrolysable, cytotoxic, ATP-analogue metabolites, inhibition of the organisation of the cytoskeleton required for the activation of the osteoclast and inhibition of the osteoclastic proton pumps).

Tiludronic acid helps in regulating bone remodelling in every situation where excessive bone resorption (i.e. increased osteoclastic activity) is occurring. Osteolysis is a painful process. In the horse, bone spavin is a condition where osteolytic leisons develop in tarsal bones, which contributes to the clinical symptoms..

In laboratory animals the regulatory effect on bone remodelling is not accompanied by negative effects on the formation and mineralisation of bone at doses sufficient to significantly inhibit bone resorption.

Pharmacodynamic data in horse free of lameness have shown that, after intravenous administration at the dose 1 mg/kg, tiludronic acid produces immediate inhibitory effects on bone resorption, as shown by the sharp decrease of a serum marker of bone resorption (CTX-1) 12 to 24 hours after dosing. Tiludronic acid was also shown to prevent the loss of bone density after a period of immobilisation by casting.

At therapeutic doses, bone formation was not impaired as shown by the absence of significant changes in the blood concentrations of a marker of bone formation (Bone alkaline phosphatase).
Tiludronic acid has also been shown to have anti-arthritic properties in a polyarthritis model in the rat. *In vitro* studies have revealed that the product has inhibitory effects on the secretion of enzymes degrading the cartilaginous matrix produced by the chondrocytes and the synovial cells.

Pharmacokinetic particulars

The pharmacokinetic profile of tiludronic acid in plasma after intravenous administration by infusion over 30 minutes in the horse at a dose of 1 mg/kg/day is characterised by a rapid decrease in plasma concentrations. Cmax is about 8 ± 2 mg/l, plasma $t_{1/2}$ is short, about 37 ± 20 hours, and total clearance is about 0.03 ± 0.01 l/h/kg. There is no plasma accumulation of tiludronic acid when infusions are repeated 3 times at 14-day intervals. The pharmacokinetic profile of tiludronic acid is dose-proportional and time-independent.

Binding to plasma proteins is of about 80% - 85%.
Tiludronic acid is rapidly cleared from blood and stored in the bone where it preferentially binds to the active remodelling sites, by binding to hydroxyapatite crystals. The bound quantity corresponds to 30 to 50% of the total administered dose. The distribution of tiludronic acid in the bone is not uniform. Binding is greater in cancellous bone than in cortical bone.

The distribution of the drug in all other body tissues is limited. It is not metabolised.

Tiludronic acid is eliminated mainly via the urine, in unchanged form**.**

Packaging

Clear glass (type II) vial with chlorbutyl rubber closure secured by aluminium overseal with plastic flip-off cap within cardboard carton.

POM-V To be supplied only on veterinary prescription

Approved: 03 March 2022