SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tildren 500 mg lyophilisate for solution for infusion for horses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Active substance:

Tiludronic acid (as disodium salt) 500 mg

After reconstitution: 1 ml solution contains 20 mg tiludronic acid.

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Mannitol (E421)	/

Lyophilisate for solution for infusion.
Compact freeze-dried white powder.

3. PHARMACEUTICAL FORM

Lyophilisate for solution for infusion.
Compact freeze-dried white powder

4. CLINICAL PARTICULARS

4.1 Target species

Horses over 3 years of age.

4.2 Indications for use, specifying the target species

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

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
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 horses with impaired renal function. Renal function should ideally be evaluated prior to treatment.
Do not use in pregnant or lactating mares (see section 3.7).
Do not use in horses producing milk for human consumption (see also section 3.12).

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for safe use in the target species:

The clinical effect of the veterinary medicinal 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.

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 speed 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 horses with disorders of heart function. In this case, it is advisable to slow down the speed of infusion.

Adequate access to drinking water should be provided when using the product. If uncertainty exists about renal function, renal parameters should be assessed before administration of the product. Water consumption and urine output should be monitored after administration.

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 case of accidental 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.

Special precautions for the protection of the environment:

Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Horse:

Common (1 to 10 animals / 100 animals treated):	Colic[1] Discomfort[2] (belly watching, yawning, pawing or kicking, stretching, light bruxism) Restlessness[2] Increased sweating Soft stool
Rare (1 to 10 animals / 10,000 animals treated):	Acute renal failure[3]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reaction[4] Anaphylaxis[4]
Undetermined frequency (cannot be estimated from the available data):	Recumbency[5]

[1] Signs of colic appear within a few hours following treatment, are mild and generally resolve without any specific treatment. In case signs persist, conventional treatments should be administered. The administration of an alpha 2 adrenergic agonist prior infusion may reduce the occurrence of signs of colic.
[2] An increase in frequency of signs of discomfort and restlessness is observed when the infusion duration is less than 15 minutes.

[3] may occur within 1 week after administration. Renal parameters should be monitored before administration and water consumption and urine output should be monitored where possible after administration. Renal insufficiency is more frequently observed in animals concurrently exposed to NSAIDs. In these cases, appropriate fluid therapy should be instituted, and renal parameters monitored.
[4] signs of reaction ranged from urticaria to anaphylactic shock, which can be fatal. A ppropriate treatment should be sought immediately.
[5] may occur after the infusion. Care should be taken to ensure that the horse can lie down in a comfortable, unrestricted area.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

4.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. The use is not recommended during 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.

4.8 Interaction with other medicinal products and other forms of interaction

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).

Concurrent administration of potentially nephrotoxic substances, such as NSAIDs,

should be approached with caution and renal function should be monitored.

No information is available on the safety and efficacy of this veterinary medicinal product when used with any other veterinary medicinal product.

4.9 Amounts to be administered and administration route

Intravenous infusion after reconstitution and dilution.

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

To ensure a correct dosage, body weight should be determined as accurately as possible.

Preparation of the ready-to-use solution for infusion:

- 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. The concentrate appears as a clear, particle free and colourless solution.
- Adhering to strict aseptic technique, inject the reconstituted solution immediately 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.
- Each vial is for single use only. Cloudy solutions or solutions containing visible solid particles should not be administered.

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.

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

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.

4.11 Withdrawal period(s)

Meat and offal: zero days

Not authorised for use in animals producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Bisphosphonates.

ATCvet code: QM05BA05.

5.1 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 lesions 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.

5.2 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421).

6.2 Major incompatibilities

Do not mix or concomitantly administer intravenously the reconstituted solution with solutions containing divalent metal ions (Ca^{2+} or Mg^{2+}) 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.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.

After reconstitution and dilution according to directions, the product may be stored at 2 to 8°C for no longer than 24 hours

6.4 Special precautions for storage

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

6.5 Nature and composition of immediate packaging

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

Pack size: 1 vial

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

7. MARKETING AUTHORISATION HOLDER

AUDEVARD
37-39 rue de Neuilly
92110 Clichy
France

8. MARKETING AUTHORISATION NUMBER

Vm 44684/5003

9. DATE OF FIRST AUTHORISATION

30 December 2015

10. DATE OF REVISION OF THE TEXT

June 2024

PROHIBITION OF SALE, SUPPLY AND/OR USE

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCT

Veterinary medicinal product subject to prescription.

Find more product information by searching for the ‘Product Information Database’ or ‘PID’ on www.gov.uk.

Gavin Hall

Approved 22 June 2024