1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Osphos 51 mg/ml solution for injection for horses (AT, BE, CZ, DE, ES, FI, FR, HU, IE, IS, IT, LU, NL, PL, PT, SE, SK, UK (NI))

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Clodronic acid 51.00 mg
(Equivalent to clodronate disodium tetrahydrate 74.98 mg)

Excipients:

Qualitative composition of excipients and other constituents
Sodium hydroxide (for pH adjustment)
Water for injections

Clear, colourless solution, practically free from visible particles.

3. CLINICAL INFORMATION

3.1 Target species

Horses.

3.2 Indications for use for each target species

For the alleviation of clinical forelimb lameness associated with the bone resorptive processes of the distal sesamoid (navicular bone) in adult horses.

3.3 Contraindications

Do not use in horses less than 4 years of age, due to the absence of data regarding use in growing animals.
Do not use in horses with impaired renal function.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not administer intravenously.

3.4 Special warnings

The veterinary medicinal 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.
Clinical improvement in lameness grade may not be accompanied by radiographic changes in the appearance of the navicular bone.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use caution when administering bisphosphonates to horses with conditions affecting mineral or electrolyte homeostasis, e.g. hyperkalaemic periodic paralysis, hypocalcaemia.
Adequate access to drinking water should be provided when using the veterinary medicinal product. If uncertainty exists about renal function, renal parameters should be assessed before administration of the veterinary medicinal 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:

Accidental self-injection of this veterinary medicinal product may increase the risk of obstructed labour in pregnant women and affect fertility in men.
Care should be taken when handling the veterinary medicinal product to avoid self-injection.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Horses:

Common (1 to 10 animals / 100 animals treated):	Nervous Lip licking, Colic Increased yawning
Uncommon (1 to 10 animals / 1,000 animals treated):	Head bobbing Injection site swelling[a], Injection site pain[a] Pawing Hives Pruritus
Rare (1 to 10 animals / 10,000 animals treated):	Renal insufficiency[b]

[a] Transient.

[b] More frequently observed in animals concurrently exposed to NSAIDs. In these cases, appropriate fluid therapy should be instituted and renal parameters monitored.

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.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy or lactation.

Pregnancy and lactation:
The use is not recommended during pregnancy or lactation.

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic or foetotoxic effects.
Laboratory studies in rats and rabbits have shown evidence of maternotoxic effects, especially during late gestation stages.

3.8 Interaction with other medicinal products and other forms of interaction

Medications such as aminoglycosides whose toxicity can be exacerbated by a reduction in serum calcium, and medications such as tetracyclines that can reduce serum calcium should not be given for 72 hours after administration of clodronic acid. Concurrent administration of potentially nephrotoxic drugs, such as NSAIDs, should be approached with caution and renal function should be monitored.

3.9 Administration routes and dosage

Intramuscular use.
1.53 mg clodronic acid per kg bodyweight, corresponding to 3 ml of the veterinary medicinal product per 100 kg body weight. Divide the total volume evenly for administration at 2 to 3 separate injection sites.
The maximum dose is 765 mg clodronic acid per horse (one 15 ml vial per horse >500 kg). Do not exceed the recommended dose.

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

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Adverse reactions may occur when the dose is exceeded. At 2X, 3X and 5X the dose, flehming, head shaking, neck retching, pawing, agitation, depression, muscle fasciculation and colic may be observed. A dose related trend for increases in blood urea nitrogen (BUN) and creatinine may also occur. At 5X dosing of clodronic acid, 3 out of 6 horses developed temporary gait abnormalities including hypermetria, spasticity or mild ataxia. Erosions of the glandular mucosa have been observed in 2 out of 8 animals administered 3X the recommended treatment dose. This was not observed in the 1X or 2X groups.
In one of 8 horses administered 3X the recommended treatment dose a 3 cm diameter area of muscle atrophy was observed at one of the injection sites.
In a clinical safety study conducted in 48 animals, signs of colic were observed in 94% of animals administered 3X the recommended treatment dose. In most cases, repeated hand walking was adequate to alleviate symptoms. Monthly administration of a 1X dose for a total of six months did not lead to signs of overdose.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal periods

Meat and offal: Zero days.
Not authorised for use in animals producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QM05BA02

4.2 Pharmacodynamics

Clodronic acid is a geminal bisphosphonate that inhibits bone resorption by binding to hydroxyapatite crystals (inhibiting their formation and dissolution), and by direct cellular effects on osteoclasts

(inhibiting osteoclast cell function). It has a high affinity for solid-phase calcium phosphate and therefore accumulates in bone, where it inhibits the formation, aggregation and dissolution of calcium phosphate crystals. Bound to bone matrix, clodronic acid enters resorbing osteoclasts, alters their morphology and reduces the number of active osteoclasts, regardless of the cause of osteoclast activity. Clodronic acid increases bone mass by inhibiting bone resorption and retarding bone turnover.

4.3 Pharmacokinetics

The pharmacokinetic profile after a single intramuscular administration of 765 mg clodronic acid in horses diagnosed with navicular syndrome is characterised by rapid absorption of clodronic acid and a longer terminal elimination phase. The plasma half-life is approximately 11.8 ± 12.5 hours (mean ± standard deviation), C_{max} is 7.5 ± 1.7 µg/mL and time to maximum concentration (T_{max}) is approximately 0.6 hours.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: use immediately.
For single use only; any remaining product should be discarded.

5.3 Special precautions for storage

Do not store above 30 °C.
Keep the container in the outer carton.

5.4 Nature and composition of immediate packaging

Clear glass (type I) vial with siliconized rubber stopper, an aluminium seal and a plastic flip-off cap containing 15 ml of clodronic acid solution.
Each cardboard box contains 1 vial.

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

Medicines should not be disposed of via wastewater or household waste.

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.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

{CARDBOARD BOX}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Osphos 51 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

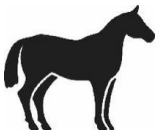
Clodronic acid 51 mg
(Equivalent to clodronate disodium tetrahydrate 74.98 mg)

3. PACKAGE SIZE

15 ml

4. TARGET SPECIES

Horses.



5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramuscular use.

7. WITHDRAWAL PERIODS

Withdrawal period:
Meat and offal: Zero days.
Not authorised for use in animals producing milk for human consumption.

8. EXPIRY DATE

Exp. {mm/yyyy}
Once broached use immediately.

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 30 °C.
Keep the container in the outer carton.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

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

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

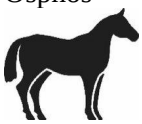
Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{VIAL LABEL}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Osphos



2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Clodronic acid 51 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}
Once broached use immediately.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Osphos 51 mg/ml solution for injection for horses

2. Composition

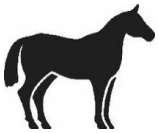
Each ml contains:

Active substance:
Clodronic acid 51 mg
(Equivalent to clodronate disodium tetrahydrate 74.98 mg)

Clear, colourless solution, practically free from visible particles.

3. Target species

Horses.



4. Indications for use

For the alleviation of clinical forelimb lameness associated with the bone resorptive processes of the distal sesamoid (navicular bone) in adult horses.

5. Contraindications

Do not use in horses less than 4 years of age, due to the absence of data regarding use in growing animals.
Do not use in horses with impaired renal function.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not administer intravenously.

6. Special warnings

Special warnings:
The veterinary medicinal product should be used only after a proper lameness examination (including nerve and/or joint blocking), combined with appropriate imaging, in order to identify the cause of pain and the nature of bone lesions. Clinical improvement in lameness may not be accompanied by improvement in the radiological appearance of the navicular bone.

Special precautions for safe use in the target species:
Use caution when administering bisphosphonates to horses with conditions affecting mineral or electrolyte regulation systems, e.g. hyperkalaemic periodic paralysis, hypocalcaemia.
Adequate access to drinking water should be provided when using the veterinary medicinal product. If uncertainty exists about renal function, renal parameters should be assessed before administration of

the veterinary medicinal 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:
Accidental self-injection of this veterinary medicinal product may increase the risk of obstructed labour in pregnant women and affect fertility in men.
Care should be taken when handling the veterinary medicinal product to avoid self-injection.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy or lactation.
The use is not recommended during pregnancy or lactation.
Laboratory studies in rats and rabbits have shown evidence of maternotoxic effects, especially during late gestation stages.
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic or foetotoxic effects.

Interaction with other medicinal products and other forms of interaction:
Medications such as antibiotics of the aminoglycoside group whose toxicity can be exacerbated by a reduction of blood (serum) calcium levels, and medications such as antibiotics of the tetracycline group that can reduce blood (serum) calcium levels, should not be given for 72 hours after administration of clodronic acid.
Concurrent administration of potentially nephrotoxic drugs, such as NSAIDs, should be approached with caution and renal function should be monitored.

Overdose:
Adverse reactions may occur when the dose is exceeded. At 2X, 3X and 5X the dose, flehming, head shaking, neck retching, pawing, agitation, depression, muscle twitching and colic may be observed. A dose related trend for increases in blood urea nitrogen (BUN) and creatinine may also occur. At 5X dosing of clodronic acid, 3 out of 6 horses developed temporary gait abnormalities including hypermetria, spasticity or mild ataxia.
Erosions of the glandular mucosa of the stomach have been observed in 2 out of 8 animals administered 3X the recommended treatment dose. This was not observed in the 1X or 2X groups.
In 1 of 8 horses administered 3X the recommended treatment dose a 3 cm diameter area of muscle atrophy was observed at one of the injection sites.
In a clinical safety study conducted in 48 animals, signs of colic were observed in 94% of animals administered 3X the recommended treatment dose. In most cases, repeated hand walking was adequate to alleviate symptoms.
Monthly administration of a 1X dose for a total of six months did not lead to signs of overdose.

Major incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

7. Adverse events

Horses:

Common (1 to 10 animals / 100 animals treated):	Nervous Lip licking, Colic Increased yawning
Uncommon (1 to 10 animals / 1,000 animals treated):	Head bobbing Injection site swelling[a], Injection site pain[a] Pawing

	Hives Pruritus (itching)
Rare (1 to 10 animals / 10,000 animals treated):	Renal insufficiency[b]

[a] Transient.
[b] More frequently observed in animals concurrently exposed to NSAIDs. In these cases, appropriate fluid therapy should be instituted and renal parameters monitored.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national system details}.

8. Dosage for each species, routes and method of administration

Intramuscular use.
1.53 mg clodronic acid per kg body weight, corresponding to 3 ml per 100 kg body weight.
The maximum dose is 765 mg clodronic acid per horse (one 15 ml vial per horse >500 kg). Do not exceed the recommended dose.

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

9. Advice on correct administration

Divide the total volume evenly for administration at 2 to 3 separate injection sites.

10. Withdrawal periods

Meat and offal: Zero days.
Not authorised for use in animals producing milk for human consumption.

11. Special storage precautions

Keep out of the sight and reach of children.

Do not store above 30 °C.
Keep the container in the outer carton.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and vial label after Exp. The expiry date refers to the last day of that month.

Shelf life after first opening the immediate packaging: use immediately.
For single use only; any remaining product should be discarded.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

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 applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

One 15 ml vial per cardboard box.

15. Date on which the package leaflet was last revised

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder and manufacturer responsible for batch release and contact details to report suspected adverse reactions:

Manufacturer responsible for batch release:
Eurovet Animal Health BV
Handelsweg 25
5531 AE Bladel
The Netherlands

Local representatives and contact details to report suspected adverse reactions:

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

17. Other information