ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Osphos 51 mg/ml solution for injection for horses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution, practically free from visible particles.

4. CLINICAL PARTICULARS

4.1 Target species

Horses.

4.2 Indications for use, specifying the target species

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

4.3 Contraindications

Do not administer intravenously.
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 known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

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.

4.5 Special precautions for use

Special precautions for use in animals:
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 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:
Accidental self-injection of this product may increase the risk of obstructed labour in pregnant women and affect fertility in men.
Care should be taken when handling the 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.

4.6 Adverse reactions (frequency and seriousness)

In a clinical field study, administration of clodronic acid at 1.19 mg/kg to 142 horses resulted in the following frequency of adverse reactions: nervousness, lip licking, yawning and colic were common; head bobbing, transient swelling and/or pain at the injection site, pawing the ground, hives and pruritus were uncommon.
Episodes of renal insufficiency have been reported, rarely, during the post-authorisation period, and were more frequently observed in animals concurrently exposed to NSAIDs. In these cases, appropriate fluid therapy should be instituted and renal parameters monitored.
The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals displaying adverse reactions during the course of one treatment)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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

4.8 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.

4.9 Amounts to be administered and administration route

Intramuscular injection only. 1.53 mg clodronic acid per kg bodyweight, corresponding to 3 ml of the 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.

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

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.

4.11 Withdrawal period

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Bisphosphonate, Clodronic acid.
ATCvet code: QM05BA02

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic particulars

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 $\pm$ 12.5 hours (mean ± standard deviation), C_{max} is 7.5 $\pm$ 1.7 µg/mL and time to maximum concentration (T_{max}) is approximately 0.6 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Major Incompatibilities

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

6.3 Shelf life

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

6.4. Special precautions for storage

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

6.5 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.

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

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

7. MARKETING AUTHORISATION HOLDER

Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
Netherlands

8. MARKETING AUTHORISATION NUMBER

IE: VPA22622/016/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

IE: 03 September 2015

Date of last renewal: 03 September 2020

10. DATE OF REVISION OF THE TEXT

January 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Osphos 51 mg/ml solution for injection for horses
Clodronic acid

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains: Clodronic acid 51 mg

3. PHARMACEUTICAL FORM

Solution for injection.

4. PACKAGE SIZE

15 ml

5. TARGET SPECIES

Horses

6. INDICATION

7. METHOD AND ROUTE(S) OF ADMINISTRATION

IM
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

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

9. SPECIAL WARNING(S), IF NECESSARY

[Read the package leaflet before use].

10. EXPIRY DATE

EXP: {month/year}
Once broached use immediately.

11. SPECIAL STORAGE CONDITIONS

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

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

[Read the package leaflet before use.]

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

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

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

IE: VPA22622/016/001 POM

17. MANUFACTURER'S BATCH NUMBER

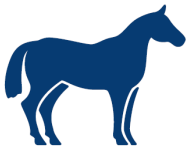
Lot:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Osphos 51 mg/ml solution for injection
Clodronic acid



2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

51 mg/ml

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

15 ml

4. ROUTE(S) OF ADMINISTRATION

IM

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot:

7. EXPIRY DATE

EXP: {month/year}
Once broached use immediately.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

IE: VPA22622/016/001 POM

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:
Osphos 51 mg/ml
Solution for injection for horses

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

Marketing authorisation holder:
Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
Netherlands

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

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Osphos 51 mg/ml solution for injection for horses
Clodronic acid

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

1 ml contains:
Active substance: Clodronic acid 51 mg
(Equivalent to clodronate disodium tetrahydrate 74.98 mg)
Clear, colourless solution for injection.

4. INDICATION

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 administer intravenously.
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 known hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

In a clinical field study, administration of clodronic acid at 1.19 mg/kg to 142 horses resulted in the following frequency of adverse reactions: nervousness, lip licking, yawning and colic were common; head bobbing, transient swelling and/or pain at the injection site, pawing the ground, hives and pruritus were uncommon.

Episodes of renal insufficiency have been reported, rarely, during the post-authorisation period, and were more frequently observed in animals concurrently exposed to NSAIDs. In these cases, appropriate fluid therapy should be instituted and renal parameters monitored.
The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals displaying adverse reactions during the course of one treatment)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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 inform your veterinary surgeon.

7. TARGET SPECIES

Horses.

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

Intramuscular injection only. 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.

9. ADVICE ON CORRECT ADMINISTRATION

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

10. WITHDRAWAL PERIOD

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. The expiry date refers to the last day of that month.
Once broached use immediately.
For single use only; any remaining product should be discarded.

12. SPECIAL WARNINGS

Special warnings for each target species:
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 use in animals:
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 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.

User warnings:
Accidental self-injection of this product may increase the risk of obstructed labour in pregnant women and affect fertility in men.
Care should be taken when handling the 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:
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.
The safety of the veterinary medicinal product has not been studied in pregnant or lactating mares. The use of the product during pregnancy or lactation in mares is not recommended.

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 (symptoms, emergency procedures, 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 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.

Incompatibilities:

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

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

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

January 2021

15. OTHER INFORMATION

IE: VPA22622/016/001 | POM | Prescription Only Medicine

One 15 ml vial per cardboard box.
For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder: