To evaluate the effectiveness of OSPHOS (clodronic acid) in controlling the clinical signs associated with navicular syndrome and to assess the clinical safety of the product.

**Objective:**

Main inclusion criteria
- Unilateral or bilateral forelimb lameness attributed to navicular syndrome
- Clinical lameness evaluation and assignment of AAEP lameness score ≥ Grade 2
- Diagnostic nerve block
  - Positive response to distal palmar digital nerve block
- Radiographic evidence of degenerative changes associated with navicular syndrome
  - Elevated number and/or abnormally shaped synovial invaginations, subcortical sclerosis, enthesiophyte formation, etc.

Main Exclusion criteria
- Hind limb lameness or musculoskeletal conditions that could have confounded the lameness exams
- Pregnant or lactating
- Age < 4 years
- Evidence or history of previous neurectomy
- Radiographic findings indicative of other disease in the foot
- NSAIDs in the 7 days prior to study initiation
- Corticosteroid treatment during the 30-day period before study initiation
- Change of shoeing pattern within two weeks before enrolment (type of foot trimming and shoeing pattern for the front feet were required to remain the same for the duration of the study)

**Study design**
- Randomised, double-blind, placebo controlled
- Multi-centre (Germany 1, US 5)
- Good Clinical Practice Guidelines
- Informed consent of owners

**Horses**
- 146 client-owned horses of various breeds enrolled
- 114 horses in the results at Day 56
- Age: 4 - 22 years
- Weight: 367 – 601 kg
- Gender: stallions, mares and geldings

**Treatments**
- Horses were enrolled in a 3:1 ratio of Osphos : placebo
- Clodronic acid (N=111): 1.19 mg/kg, Maximum dose: 765 mg/horse (15 mL of Osphos) (1 mg clodronic acid is equivalent to 1,176 mg disodium clodronate)
- Placebo control (N=35): 0.9% saline at equivalent volume, Maximum dose: 15 mL
- Administered on Day 0 intramuscularly at 3 injection sites
- Option of a compassionate use treatment of known clodronic acid at Day 56. These horses were excluded from Day 180 effectiveness evaluation
Efficacy criteria

**Primary outcome: clinical effectiveness**

Improvement of lameness of at least one grade (AAEP 0-5) in the limb with the most apparent lameness. Plus no worsening of lameness grade due to navicular syndrome in the “least lame” forelimb as compared to the baseline value. Evaluations at Day 28, 56, 180.

Results

75% of horses responded positively to treatment with Osphos at Day 56, which was highly statistically significant compared to the control group (*p*-value = 0.0028).

Most horses were enrolled with a lameness score of 3 or 2, which had improved to 2, 1 or 0 by Day 56.

### Success rate during the study

<table>
<thead>
<tr>
<th></th>
<th>Day 28</th>
<th>Day 56</th>
<th>Day 180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opshos</td>
<td>67%</td>
<td>75%*</td>
<td>65%</td>
</tr>
<tr>
<td>Placebo</td>
<td>21%</td>
<td>3%*</td>
<td></td>
</tr>
</tbody>
</table>

Day 180: Total reference population = 60 horses evaluable (these were treatment successes at Day 56) + 18 treatment failures Day 56.

Adverse events

- All 146 enrolled horses included in the safety assessment
- None terminated the study as a result of adverse events
- All adverse events were mild, transient and self-limiting
- For type and incidence of adverse events please consult the SPC
- No clinically relevant changes were seen in the haematology or blood biochemistry

Conclusions

- Horses treated with clodronic acid had a significantly higher success rate than horses treated with placebo
- 75% of horses responded positively to Osphos treatment at Day 56
- Horses showed improvement as early as day 28 after treatment (1st control)
- 2/3 of treated horses showing at least 6 months of improvement after single treatment

References

Frevel et al. (2014), Multi-centre field trial to evaluate the effectiveness of clodronic acid for navicular syndrome. Equine Vet J 2014; 46, Suppl.47

Osphos Publicly Available Assessment Report for a Veterinary Medicinal Product, VMD, UK

www.dechra.co.uk/osphos
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT
Ophos 57 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 dihydrate 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 fore limb 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 administer to horses less than 4 years of age, due to the absence of data regarding use in growing animals.
Do not administer to 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.

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 at the injection site, pawing the ground, hives and pruritus were uncommon.
The frequency of adverse reactions is defined using the following convention:
- 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)

4.7 Use during pregnancy and lactation
Laboratory studies in rats and rabbits have shown evidence of teratogenic 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 is not recommended.

4.8 Interaction with other medicinal products and other forms of interaction
Bisphosphonates are known to cause bone resorption in a number of species. This effect is believed to be due to the inhibition of osteoclast activity. The net effect of bisphosphonates on bone may be variable and depends on the duration of treatment.

4.9 Amounts to be administered and administration route

Intramuscular injection only. 1.53 mg clodronic acid per kg body weight, corresponding to 3 ml per 100 kg body weight. Dose 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, fever, shivering, head shaking, neck rectching, 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 of 6 horses developed temporary mild abnormalities including hypermetria, spasticity or mild ataxia. Emissions of the gingival 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 general 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 plasma half-life 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). Cmax is 7.5 ± 1.7 µg/ml and time to maximum concentration (Tmax) is approximately 0.6 hours.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium hydroxide (for pH adjustment)
Water for injections

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

6.3 Shelf life
Short shelf life of the veterinary medicinal product as packaged for sale: 2 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 chlorobutyl 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 Limited
Stargill Industrial Estate, Kirbyby Road, Skipton North Yorkshire, BD23 2RW United Kingdom

8. MARKETING AUTHORISATION NUMBER
UK: Vm 10434/4086
IE: VPA 10799/029/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02 September 2015

10. DATE OF REVISION OF THE TEXT
September 2015