The intramuscular bisphosphonate injection for control of clinical signs associated with navicular syndrome in horses 4 years of age and older.
WHAT IS A bisphosphonate?

Bisphosphonates are a class of drugs commonly prescribed to prevent bone loss. Bisphosphonates have been used for decades in human medicine to treat a variety of resorptive conditions, such as osteoporosis, osteopenia, and malignant bone neoplasia. While OSPHOS® (clodronate injection) is not used for this purpose in horses, knowing how bisphosphonates work in people will help you better understand this drug class, including the clinical efficacy and safety margins.

Bones undergo constant turnover, with osteoblasts forming bone and osteoclasts resorbing it. In normal bone tissue, there is a balance between bone formation and bone resorption; however, in diseased bone tissue, this balance is disrupted. Bisphosphonates inhibit bone resorption by encouraging osteoclasts to undergo cell death, leading to a decrease in the breakdown of bone.

Bisphosphonate drugs are characterized by a chemical structure that gives them the unique ability to bind to bone mineral and become internalized by osteoclasts. Bisphosphonates preferentially “stick” to calcium and bind to it. Because most of the body’s calcium is stored in bones, these drugs accumulate to a high concentration only in bones. Bisphosphonates are incorporated into the bone mineral and are gradually released over months to years.
There are two types of bisphosphonates, nitrogenous (complex, nitrogen-containing) and non-nitrogenous (simple, non-nitrogen containing).

The mechanism of action of these molecules is supremely dependent on the biochemical structure and whether the bisphosphonate group is simple or complex. Complex, nitrogenous bisphosphonates work via inhibition of the mevalonate pathway, which is involved in production of lipids and proteins responsible for complex cell signaling.

Simple, non-nitrogenous bisphosphonates, such as OSPHOS, act at several key places within the osteoclast-producing pathway. They can inhibit osteoclast recruitment, adhesion, differentiation, and resorptive activity, and induce apoptosis, or cell death.

Non-nitrogenous bisphosphonates are metabolized into osteoclasts and incorporated into ATP molecules, creating cytotoxic ATP. Cytotoxic ATP accumulates within osteoclasts, inhibiting morphology, metabolism and cellular function to induce apoptosis.²

Osphos given at the labeled FDA-approved dose does not affect CTX-1 or osteocalcin serum blood levels. Decreases in CTX-1 levels in humans have been associated with bisphosphonate-related atypical fractures.

A single dose of clodronate reduces forelimb lameness without producing detectable effects on the bone biomarkers CTX-1 and osteocalcin.³
Navicular syndrome is a bone resorptive condition.
As horses with navicular syndrome undergo loss of bone experimentally, as well as clinically, treatment with OSPHOS® (clodronate injection) is effective at controlling the clinical signs associated with navicular syndrome in horses 4 years and older.

How efficacious is OSPHOS?
Over the 6-month field efficacy study, OSPHOS was demonstrated to be effective in controlling the clinical signs associated with navicular syndrome by decreasing the lameness grades of affected horses. On day 56, 68/86 OSPHOS treated horses and 1 out of the 28 saline treated horses were treatment successes.

For horses that initially respond to OSPHOS but don’t maintain their clinical improvement for 6 months, you may administer the drug at 3-6 month intervals based on clinical signs. If there is no response to initial therapy the horse should be re-evaluated.

How is OSPHOS administered
Administer 1.8 mg/kg by intramuscular injection (IM) up to a maximum permissible dose of 900 mg per horse. Divide the total volume evenly into three separate injection sites. Discard any unused portion of the vial since OSPHOS does not contain a preservative.

Precautions and side effects
Bisphosphonates, such as OSPHOS, have been associated with renal toxicity. Concurrent administration of other potentially nephrotoxic drugs, such as NSAIDs and sedatives, should be approached with caution and renal function should be monitored both externally and internally where appropriate. NSAIDs should not be given concurrently with OSPHOS and a wash-out period of NSAIDs should be 2-3 days prior to and after administration.

Horses should be well-hydrated prior to and after the administration of OSPHOS due to the potential for adverse renal events. Water intake and urine output should be monitored for 3-5 days post-treatment and any changes from baseline should elicit further evaluation.

As with all drugs, side effects may occur. In field studies and post-approval experience the most common side effects reported were signs of discomfort, nervousness, and colic. Other signs reported were: renal insufficiency/failure, anorexia, lethargy, hypercalcemia, behavioral disorders, hyperkalemia, hyperactivity, recumbency, hyperthermia, injection site reactions, muscle tremor, urticaria, hyperglycemia, and fracture. In some cases, death has been reported as an outcome of these adverse events.

The safe use of OSPHOS has not been evaluated in horses less than 4 years of age or breeding horses. OSPHOS should not be used in pregnant or lactating mares, or mares intended for breeding. NSAIDs should not be used concurrently with OSPHOS. Concurrent use of NSAIDs with OSPHOS may increase the risk of renal toxicity and acute renal failure. Use of OSPHOS in patients with conditions affecting renal function or mineral or electrolyte homeostasis is not recommended. Refer to the prescribing information for complete details or visit www.dechra-us.com.
REFERENCES

OSPHOS (clodronate injection)

Bisphosphonates

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>OSPHOS (n=11)</th>
<th>Control (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomfortable, Necros. Cells, and/or Pawing</td>
<td>9 (90.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lameness</td>
<td>7 (77.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Yawning</td>
<td>4.5% (5)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Head shaking</td>
<td>2.7% (3)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>1.8% (2)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Colic requiring treatment*</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Hives/Pruritis</td>
<td>0.9% (1)</td>
<td>0% (0)</td>
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</tbody>
</table>

* This horse experienced colic and licks and recovered with supportive treatment.

POST-APPROVAL EXPERIENCE (December 2018): The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to TRACVR. It is not possible to reliably estimate the adverse effect frequency or severity due to the nature of the data collected using these data. The following adverse events are listed in increasing order of reporting frequency: renal failure, polyuria, polydipsia, abdominal pain, anorexia, diarrhea, vomiting, inappetence, fever, lameness, respiratory distress (up lying), coughing, dyspnea, hyperventilation, hyperthermia, restlessness, tachypnea, hypertension, injection site reactions (pain, edema, inflammation), muscle tremor, urticaria, hypoglycemia, and fracture.

In some cases, death has been reported as an outcome of the adverse events listed above (see PRECAUTIONS).

INFORMATION FOR HUMAN OWNERS: Owners should be advised to:

- Ensure horses have access to adequate water before and after administration of OSPHOS.
- Observe horses for at least 1 hour post-intramuscular injection for signs of abnormal behavior.
- Evaluate the pain response 24 hours following post-treatment, hand walk the horse for 15 minutes. If signs do not resolve contact the veterinarian.
- Contact the veterinarian if the horse displays abnormal clinical signs such as changes in drinking and urination, appetite and activity.

Table 1: Adverse Reactions Occurring within 2 Hours Post-treatment

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* This horse experienced colic and licks and recovered with supportive treatment.

CLINICAL PHARMACOLOGY:

Bisphosphonate is a non-steroidal anti-inflammatory drug (NSAID) that inhibits bone resorption and decreases bone turnover. Bisphosphonate has been shown to cause fetal developmental abnormalities in laboratory animals. The uptake of bisphosphonates into fetal bone may be greater than into maternal bone creating a possible risk for skeletal or other abnormalities in the fetus. Many drugs, including bisphosphonates, have been shown to cause acute and chronic renal failure.

Studied in clinical and field trials, OSPHOS is effective in reducing lameness scores, improving overall clinical signs, and reducing parathyroid hormone (PTH) concentrations after treatment with a single injection. The effects of OSPHOS are dose dependent.

In the field study, 65% of treated horses maintained their level of improvement through the 6 month evaluation. In the TAS study, OSPHOS was administered to 32 healthy adult horses at 0, 1.8, 3.6 and 5.4 mg/kg (9 mg/kg) dose of OSPHOS. Compared to saline control, a decrease in apparent total systemic clearance (CL/F) was seen (0.08 mL/hr + 0.02; mean + standard deviation), resulting in an increased risk for adverse reactions.

The structural formula of clodronate is:

Molecular Formula: ClOd3Na2O8P
Molecular Weight: 389.17

Active substance clodronate dl-tartrate 74.98 mg, corresponds to clodronate dl-tartrate 60.0 mg. Each mL contains 60 mg clodronate dl-tartrate, sodium hydroxide (to adjust pH) and water for injection.

INDICATIONS:

OSPHOS is indicated for the management of sarcoidic arthritis in horses.

DOSAGE AND ADMINISTRATION:

Administer 1.8 mg/kg intramuscularly up to a maximum dose of 900 mg per horse. Divide the total volume evenly to three separate injection sites. Dissard unused vial contents. OSPHOS is provided in a single use vial and does not contain a preservative.

Clinical improvement is most evident at 2 months post-treatment (see EFFECTIVENESS). If the horses that responded to treatment with OSPHOS do not respond after 6 months, OSPHOS may be administered at 3 to 6 month intervals based on recurrence of clinical signs. For horses that respond to OSPHOS and maintain clinical improvement for 6 months, OSPHOS should be re-administered after clinical signs return.

CONTRAINDICATIONS:

Horses with hypersensitivity to clodronate should not receive OSPHOS. Do not use in horses with a known or suspected mild to moderate renal disease.

WARNINGS:

Do not use in horses intended for human consumption.

NSAIDs should not be used concurrently with OSPHOS. Concurrent use of NSAIDs with OSPHOS may increase the risk of renal toxicity and mineralization of soft tissue.

Horses may develop temporary gait abnormalities. In the field study, symptoms were mild, typically resolving within hours to days. In the field study, 9.0% (10) horses experienced lameness scores of discomfort or nervousness, cramping, pawing, and/or colic within 2 hours post-treatment. Following treatment on Day 0, 10 horses had clinical signs of discomfort or nervousness, cramping, pawing, and/or colic within 2 hours post-treatment. One horse developed temporary gait abnormalities that included mild to moderate hypermetria, spasticity, or mild ataxia. Four out of six horses developed temporary gait abnormalities that included mild to moderate hypermetria, spasticity, or mild ataxia.

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OSPHOS is supplied in cartons with each carton containing one clear glass 20 mL vial with 15 mL (900 mg) clodronate dl-tartrate (9 mg/kg). OSPHOS treated horses are considered to remain treatment failures at Day 180. No Day 180 lameness evaluation was performed on these horses. 60 horses (60 OSPHOS treated horses) completed the Day 180 lameness evaluation.

The study results demonstrated that in a two phase pilot study, two were conducted to evaluate the safety of the third administration of a regimen consisting of a single 5.4 mg/kg intramuscular injection administered every 28 days. In this 3X study, 114 horses (86 OSPHOS, 28 saline control) were included in the statistical analysis. Day 56 treatment failures were considered as Day 180 failures. Of the 68 horses assigned to the OSPHOS treatment group, 65 treatment failures were recorded during Phase I of the study. In Phase II, 35 treatment failures were recorded during Phase II of the study. In total, 101 treatment failures were recorded during Phase I and Phase II of the study. Of the 65 treatment failures in Phase I of the study, 60 were resolved without hand walking. In a 3X study, 19 treatment failures were recorded during Phase I and Phase II of the study. In total, 28 treatment failures were recorded during Phase I and Phase II of the study. Of the 18 horses that were treatment failures, 6 horses were considered to remain treatment failures at Day 180. No Day 180 lameness evaluation was performed on these horses. 60 horses (60 OSPHOS treated horses) completed the Day 180 lameness evaluation.

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