NAVICULAR SYNDROME is a multifaceted disease and the treatment options are not always clear. When radiographic signs indicative of bony changes associated with navicular syndrome are present, OSPHOS is a clear choice.
The navicular bone, also known as the distal sesamoid bone, is a small bone that sits deep within the hoof and is the shape of a small canoe.

The primary function of the navicular bone is to provide a constant angle of insertion for the deep digital flexor tendon (DDFT). It serves as a fulcrum for the DDFT, similar to the way a pulley functions for a rope.

WHAT IS NAVICULAR SYNDROME?

Equine navicular syndrome is a chronic forelimb lameness associated with pain arising from the navicular bone and the closely related soft tissue structures. These structures include the collateral suspensory ligaments of the navicular bone, distal sesamoidean impar ligament, navicular bursa and the deep digital flexor tendon. When a horse has navicular syndrome, the problem can arise from the navicular bone itself, the surrounding soft tissue structures, or both.

WHAT CAUSES NAVICULAR SYNDROME?

The exact cause of navicular syndrome is unknown; however biomechanical influences are thought to be involved, causing damage to the navicular bone which leads to increased bone remodeling and destruction. One example of the biomechanical forces on the navicular bone is increased tension on the deep digital flexor tendon which results in increased pressure across the navicular bone.

Abnormal bone remodeling can change the integrity of the navicular bone causing pain and leading to further damage.

Recognizing the Signs of Navicular Syndrome

Navicular syndrome usually affects the front feet of horses causing either a low-grade unilateral or bilateral lameness, which most often progresses slowly. The lameness may only occur from time to time, or when the horse is exercised on hard ground or in a tight circle. In some cases, one foot is affected more than the other causing obvious lameness.

Signs include but are not limited to:
• Short, choppy stride
• Stumbling
• Refusal to jump
• Intermittent shifting of the lame leg
• Tip-toeing (lands toe first, instead of normal heel to toe landing)
• Increased lameness the day after work

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DIAGNOSING NAVICULAR SYNDROME
No single test can be used to diagnose navicular syndrome. Diagnosis is made after a consideration of the horse’s history, use, conformation, and test results.

Your veterinarian will do a variety of procedures to confirm your horse has navicular syndrome. First they will start with a thorough medical and lameness examination which will include:

• A visual appraisal of the horse at rest to study the horse’s conformation, balance and weight bearing; and look for any evidence of injury or stress.

• A hands-on examination of the muscles, joints, bones and tendons looking for evidence of pain, heat, swelling or any other physical abnormalities. Pulses arising from the blood vessels of the lower limb are also examined.

• Application of hoof testers to the feet. This instrument allows the veterinarian to apply pressure to specific areas of the hoof to check for sensitivity or pain.

• Evaluation of the horse in motion. Your veterinarian will observe the horse walking and trotting and if possible, they will observe the horse’s gait and attitude on a variety of ground surfaces (soft and hard).

• Flexion tests help to assess the capsule surrounding joints together with the associated ligaments, tendons, and bone ends. In an attempt to accentuate the lameness, the veterinarian will hold the limb in a flexed position for a short period of time and then release the leg. As the horse trots away, the veterinarian watches for exacerbation of lameness or abnormal tracking.

NERVE BLOCKS
Nerve Blocks, or regional anesthesia, are important because they can ‘block out’ or desensitize the pain caused by the palmar digital nerve which causes pain in horses with navicular syndrome. Your veterinarian will insert a needle near where the palmar digital nerve lies and inject a local anesthetic. If the horse was lame before the injection, and trots normally afterwards, then it may be assumed that the lameness is located in the region that was “blocked” or anesthetized.

DIAGNOSTIC TESTING
Radiographs
There are several different diagnostic tests your veterinarian might perform to confirm the diagnosis of navicular syndrome. The most common one is radiography. Usually several views are taken of the foot from varying angles. Radiographs (commonly referred to as x-rays) provide a good assessment of the bony structures of the foot and are less able to reveal changes in the soft tissues of the foot.

Magnetic Resonance Imaging (MRI)
MRI uses strong magnetic fields and radiofrequency pulses to image, with great detail, both bone and soft tissue structures deep within the foot. MRI is more sensitive for evaluating soft tissue than radiography and can help confirm a diagnosis when radiographic finding are equivocal. Disadvantages of MRI include more difficult access to the necessary equipment, cost and most often the necessity for anesthesia.

THERAPIES FOR NAVICULAR SYNDROME
After diagnosing navicular syndrome, your veterinarian might recommend medical, surgical and/or complementary therapies including:

• Bisphosphonates, such as OSPHOS
• Corrective shoeing and proper hoof trimming
• Regenerative medicine (i.e. irap, stem cells)
• Veterinary prescribed pain management
• Nutraceuticals
• Shockwave therapy

Trimming, shoeing and proper hoof care are important therapies, no matter which other therapies the horse receives.
BONE REMODELING
Navicular syndrome is known to cause stress and damage to the navicular bone leading to excessive bone remodeling. The normal bone remodeling pathway requires that bone resorption (digestion of bone) and new bone formation take place at the same site and in a coordinated fashion. Usually, the amount of bone formed during bone remodeling equals the amount destroyed. Any disruption in this balance results in disease to the bone, including bone loss.

During bone stress or disease, bone metabolism is accelerated and osteoclasts are stimulated to begin the remodeling cycle. Osteoblasts follow behind the bone-eating cells, but at a much slower pace. Accelerated bone resorption may exceed the bone rebuilding process during these times of chronic bone disease or stress, including navicular syndrome.

OSTEOCLASTS resorb bone
OSTEOBLASTS build bone

What is OSPHOS® (clodronate injection) and how is it given to my horse?
OSPHOS is an injectable bisphosphonate indicated for the control of clinical signs associated with navicular syndrome in horses 4 years and older. OSPHOS is the only bisphosphonate approved by FDA for intramuscular use in horses. Your veterinarian will administer up to one 1 vial of OSPHOS in 3 separate injection sites including the neck, pectoral muscles and/or gluteal muscles, or other sites they determine to be best.

Owners are advised to observe their horse for at least two hours post-treatment for signs of colic, agitation, and/or nervous system abnormalities. If a horse appears uncomfortable, nervous, or experiences cramping post-treatment the owner should be advised to contact their veterinarian and hand walk the horse for 15 minutes or until signs resolve.

*OSPHOS is a prescription drug product for use only by or on the order of a licensed veterinarian.

What results can I expect with OSPHOS?
In clinical trials, the statistical success rates were 74.7% for horses treated with OSPHOS (n=86) and 3.3% for horses treated with saline placebo (n=28). The difference in success rates is statistically significant (p-value of 0.0028). A horse was considered a treatment success if the lameness grade in the primarily affected limb improved by at least 1 AAEP grade and there was no worsening of lameness grade in the other forelimb on Day 56 post-treatment as compared to the pre-treatment assessment. Of the 86 horses treated with OSPHOS, eight horses had an improvement of 3 lameness grades, 45 horses improved by 2 lameness grades and 16 horses improved by one lameness grade (raw data).

If there is no response to initial therapy, your horse should be re-evaluated by your veterinarian. For horses that do respond to OSPHOS but do not maintain their clinical improvement for 6 months, OSPHOS may be given 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 recur.
Following treatment on Day 0, 10 horses had clinical signs of discomfort or nervousness, cramping, pawing, periods of time. Bisphosphonates inhibit bone resorption and decrease bone turnover which may lead to an increased bone fragility has been observed in animals treated with bisphosphonates at high doses or for long extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Bisphosphonates have 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 anatomical defects. Many drugs, including bisphosphonates, may be excreted in milk and may be absorbed by nursing animals. Increased bone fragility has been observed in animals treated with bisphosphonates at high doses or for long periods of time. Bisphosphonates inhibit bone resorption and decrease bone turnover which may lead to an inability to repair microdamage within the bone. In humans, atypical femur fractures have been reported in patients on long term bisphosphonate therapy; however, a causal relationship has not been established.

ADVERSE REACTIONS: One hundred forty-six horses (111 OSPHOS, 35 saline controls) of various breeds, 4 to 25 years of age, and weighing 807 to 1,022 pounds were included in the field study safety analysis. 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 experiencing colic and flies required treatment with flunixin and doramectin to resolve clinical signs. In 8 of the 10 horses, 10 to 15 minutes of hand walking resulted in resolution of clinical signs. In one horse, clinical signs resolved without hand walking. Three additional horses experienced lip licking, yawning, and/or head shaking. Adverse reactions occurring within 2 hours post-treatment with OSPHOS or the saline control are summarized in Table 1.

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

<table>
<thead>
<tr>
<th>CLINICAL SIGN</th>
<th>OSPHOS (n=111)</th>
<th>Control (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip licking</td>
<td>5.4% (6)</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>2.9% (1)</td>
</tr>
<tr>
<td>Colic requiring treatment*</td>
<td>0.9% (1)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Hives/Pruritus</td>
<td>0.9% (1)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

* This horse experienced colic and flies recovered after treatment with flunixin and doramectin.

To report suspected adverse events, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVets/SafetyHealth.
In the TAS study, post-treatment clinical signs also included yawning, filthmen, tongue rolling, head shaking and neck writhing. The signs were observed in 50% (48/96) of 0X, 100% (8/8) of 1X, 86% (7/8) of 2X, and 100% (8/8) of 3X horses. All horses returned to normal within 3.5 hours post-treatment.

Table 4: Incidence of Abnormal Clinical Signs in the TAS Study

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>0X</th>
<th>1X</th>
<th>2X</th>
<th>3X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colic*</td>
<td>4</td>
<td>2</td>
<td>26</td>
<td>45</td>
</tr>
<tr>
<td>Colic requiring hand walking</td>
<td>0</td>
<td>3</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Yawning</td>
<td>5</td>
<td>17</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Filthmen</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Tongue rolling</td>
<td>1</td>
<td>10</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Head shaking</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Neck writhing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pawing</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Agitation</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

* Signs of colic included repeated lying down and rising, rolling, kicking at the abdomen, stretching of the abdomen and/or other typical signs of abdominal discomfort.

Injection site reactions were identified in three 0X, four 1X, two 2X, and one 3X horse. One 1X horse had injection site reactions on two separate treatment days. Injection site reactions in OSPHOS treated horses were characterized by soft or firm swellings, ranged in size from 0.5 cm diameter to 7 x 28 cm, and resolved within 10 days. Clinical pathology evaluations showed a dose related trend for increases in BUN and creatinine post-treatment with the 2X and 3X dose groups having statistically significant elevations as compared to the 0X dose group. Horses in all OSPHOS treated groups had dose dependent elevations in BUN concentrations above the reference range (up to 41 mg/dL; reference range 8-25 mg/dL). Three 3X horses had creatinine concentrations above the reference range (up to 2.5 mg/dL; reference range 0.9-1.8 mg/dL) for up to 12 hours post treatment. A dose related trend for an increase in potassium was observed for up to 6 hours post-treatment. Individually animal potassium concentrations were within the reference range with the exception of two 0X horses with post-treatment potassium concentrations up to 5.3 mg/dL (reference range 3-5 mg/dL). Decreases in chloride and increases in glucose, creatinine, kinase, and aspartate aminotransferase were also observed post-treatment. End of study evaluations concluded that bone density (bone mineral concentration) and bone strength (mechanical testing of cortical bone) remained similar between all dose groups.

NSAIID and SX Study: In Phase I of a two phase pilot study, six horses were administered phenylbutazone orally twice a day at a dose of 4.4 mg/kg on Days 0 to 3, administered OSPHOS at 1.8 mg/kg (1X) by intramuscular injection into 3 sites once on Day 4, and continued on phenylbutazone orally twice a day at a dose of 2.2 mg/kg on Days 4 to 6. In Phase II of the pilot study, after a 15 day washout, the same six horses were administered a single dose of OSPHOS at 9 mg/kg (3X) by intramuscular injection divided evenly into 5 separate injection sites. In Phase I, three horses had post-treatment elevations in BUN above the reference range up to 42 mg/dL, reference range 8-25 mg/dL. BUN concentrations returned to normal prior to Phase II of the study. In Phase II, five out of six horses developed changes in attitude associated with signs of agitation or restlessness including pacing, circling, and tail twitching within 6 minutes of dosing. Four of six horses also developed clinical signs including excessive yawning, filthmen, tongue rolling, head shaking, and head bobbing. All six horses developed mild to moderate muscle fasciculations between 2 and 30 minutes post-treatment. By 30 minutes post-treatment, four out of six horses also developed signs of discomfort and possible abdominal pain including full body stretching, repetitive lying down and rising, and kicking at the abdomen. At approximately one hour post-treatment, one horse exhibited agitation and clinical signs of colic requiring medical therapy. The horse responded to medical therapy and was clinically normal at 7 hours post-treatment. Three out of six horses developed temporary gait abnormalities that included mild to moderate hypermetria, spasticity, or mild ataxia. Four out of six horses developed mildly elevated BUN concentrations by 48 hours post treatment and one horse had a creatinine concentration slightly above the reference range (2.0 mg/dL; reference range 0.8-1.9 mg/dL) for 12 hours post-treatment.

STORAGE INFORMATION: Store at controlled room temperature 25°C (77°F) with excursions between 15°C-30°C (59°F-86°F) permitted. Single use vial; discard unused portion.

HOW SUPPLIED: OSPHOS is supplied in cartons with each carton containing one clear glass 20 mL vial with 15 mL (900 mg) clodronate disodium (80 mg/mL) per vial.

NDC 17033-460-15

For further information about lameness in your horse visit: www.equinelameness.com and www.osphos.com or ask your veterinarian.

If you have further questions about navicular syndrome and OSPHOS please contact your veterinarian.