Dechra
Veterinary Products

FREQUENTLY ASKED QUESTIONS

OSPHOS® (clodronate injection)

1. What is OSPHOS® (clodronate injection)?

OSPHOS® (clodronate injection) is a safe and effective FDA-approved treatment marketed by Dechra Veterinary Products for the control of clinical signs associated with navicular syndrome in horses 4 years of age and older. The use of OSPHOS in horses less than 4 years of age has not been studied.

2. What is a bisphosphonate?

OSPHOS® (clodronate injection) is a member of the bisphosphonate drug class. Bisphosphonates are a group of pharmacological agents that have existed since the 1960s and are employed worldwide for osteoporosis and bone abnormalities in human medicine and research. There are two generations of bisphosphonates, non-nitrogenous (non-nitrogen containing) and nitrogenous (nitrogen-containing). OSPHOS is a first-generation non-nitrogenous bisphosphonate. This is the least potent class of bisphosphonate. The nitrogenous bisphosphonates are not approved for use in horses and work on a more complex pathway with a myriad of side effects as observed and documented in human medical literature.

3. How do bisphosphonates work?

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. But in diseased bone tissue, this balance is disrupted. The main effect of a bisphosphonate is to decrease bone resorption and bring the balance of osteoclast and osteoblast activity back to normal by reducing the activity of the osteoclasts. OSPHOS® (clodronate injection) inhibits bone resorption by binding to bone mineral (inhibiting formation and dissolution), and by exerting direct cellular effects on osteoclasts.[1]

4. How are bisphosphonates used in horses?

Bisphosphonates are used to treat navicular syndrome in horses. OSPHOS® (clodronate injection) gained approval in April 2014 by the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) as a non-nitrogenous bisphosphonate drug indicated for control of clinical signs associated with navicular syndrome in horses 4 years of age and older. OSPHOS is the only FDA-approved product containing clodronate indicated for the control of clinical signs of navicular syndrome in horses and is available exclusively through licensed veterinarians.[2] OSPHOS has gained wide acceptance in equine veterinary medicine to address navicular syndrome in an effective and non-invasive manner.

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[1] OSPHOS (clodronate injection) package insert.

[2] FDA Provides Equine Veterinarians with Important Information about TILDREN and OSPHOS for Navicular Syndrome in Horses. https://www.fda.gov/animalveterinary/resourcesforyou/ucm406581.htm (accessed 4/2/19)

5. What is navicular syndrome?

Equine navicular syndrome is one of the most common lameness issues in the adult horse. It is defined as chronic forelimb lameness associated with pain arising from the navicular bone and closely related structures including the collateral suspensory ligaments of the navicular bone, distal sesamoidean impar ligament, navicular bursa, and the deep digital flexor tendon.[3] Chronic pain associated with navicular syndrome has been reported as causing one-third of all chronic forelimb lameness in horses.[4] The syndrome affects horses of many breeds and activity groups, typically 4 to 15 years of age.[5,6] 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 bone destruction.

6. Is OSPHOS® (clodronate injection) safe for use in young horses?

The safe use of OSPHOS has not been evaluated in horses less than 4 years of age. OSPHOS has been approved for horses 4 years of age and older because navicular syndrome manifests at this age or older in the horse. The effect of bisphosphonates on the skeleton of growing horses has not been studied; however, bisphosphonates inhibit osteoclast activity which impacts bone turnover and may affect bone growth. Dechra does not promote or recommend the use of OSPHOS in horses less than 4 years of age.

7. What is Dechra doing to promote appropriate use of bisphosphonates?

Dechra firmly believes OSPHOS® (clodronate injection) is safe to use in horses when label directions are followed. We have a strong veterinary team who work collaboratively to ensure consistency, quality and ethical patient care is priority with regards to the use of OSPHOS. Dechra has undertaken significant educational efforts since the product launched to inform the profession on the indicated safe use of the product and have a very high compliance rate with on-label use of the product, particularly in English sport and western performance horses. For example, just since early 2017, the veterinary professional services team has conducted more than 280 educational presentations on OSPHOS. As an American Association of Equine Practitioners (AAEP) Educational Partner, we are committed to working with and for the industry to gain additional understanding of the drug and its use in an on-label manner.

8. What is the re-dosing interval for OSPHOS® (clodronate injection)?

OSPHOS may be re-administered at 3- to 6-month intervals based on FDA approval safety studies. The exact timing of the re-dosing is variable based upon each case. Dechra recommends re-dosing be determined by an attending veterinarian who can evaluate recurrence of clinical signs.

9. What is the detection time for OSPHOS® (clodronate injection)?

The Federation Equestre Internationale (FEI) has listed clodronate, a non-nitrogenous bisphosphonate, as a controlled substance for competing horses, but so far has not published a specific detection time. FEI has published a detection time of 28 days for tiludronate, a non-nitrogenous bisphosphonate similar to clodronate. Dechra supports the 28-day withdrawal period for bisphosphonates as instituted by FEI.

[3] Adam's and Stashak's lameness in horses-6th ed./ [edited by] Gary M. Baxter. Wiley-Blackwell, West Sussex, UK 2011; pp 475-593.
[4] Adam's and Stashak's lameness in horses-6th ed./ [edited by] Gary M. Baxter. Wiley-Blackwell, West Sussex, UK 2011; pp 475-593.
[5] Colles, CM. Navicular Disease and Its Treatment. In Practice 1982; 4:29-36.
[6] Dyson, SJ. Navicular disease and other soft tissue causes of palmar foot pain. In Diagnosis and Management of Lameness in the Horse. Ross MW, Dyson SJ, eds. Saunders, St. Louis, MO 2003; 286-298.

Dechra is actively working with an established equine testing laboratory and is beginning an on-label detection study in sport horses who are actively "working" and have navicular disease.

The British Horseracing Authority (BHA) has announced a stand-down period for veterinary licensed bisphosphonates (tiludronate and clodronate) of 30 days. The Canadian Pari-Mutuel Agency (CPMA) has set an elimination guideline of 30 days for horses four years of age and older. Dechra recommends referring to existing rules and regulations governing medication use and consult other jurisdictions and organizations for guidance. For information regarding laboratories available to perform OSPHOS detection analysis Dechra recommends discussing directly with national and international jurisdictions and organizations who have implemented withdrawal times in an effort to ensure confidence in variable substance detection methods, assay results, and interpretation.

10. Is OSPHOS® (clodronate injection) safe for horses intended for breeding?

The safe use of OSPHOS has not been evaluated in pregnant or lactating mares or mares intended for breeding. Bisphosphonates have been shown to cause abnormal fetal development in laboratory animals. The uptake of bisphosphonates into fetal bone may be greater than into maternal bone, creating a possible risk of skeletal or other abnormalities in the fetus. Bisphosphonates may be excreted in milk and absorbed by nursing animals. Although stallions were included in our (Dechra) field efficacy study, effects of OSPHOS on fertility were not studied. Dechra does not promote or recommend the use of OSPHOS in pregnant or lactating mares or horses intended for breeding.

11. What are the known common side effects of OSPHOS® (clodronate injection)?

The majority of adverse events associated with the labeled use of OSPHOS have been mild and self-limiting. Clinical signs exhibited are usually mild and transient and have included symptoms of abdominal pain (colic), discomfort, and agitation.

Bisphosphonates can cause renal toxicity. Higher blood plasma levels may increase the risk of toxicity. Bisphosphonates are excreted by the kidneys, therefore conditions and or medications that impair renal function may increase the blood plasma level and lead to more adverse reactions. Dechra does not recommend the use of OSPHOS in horses with impaired renal function. For additional safety information, please see full prescribing information.

12. Can OSPHOS® (clodronate injection) be used with NSAIDs?

Dechra does not consider it necessary nor recommends pre-medication with a nonsteroidal anti-inflammatory drug (NSAID). Furthermore, pre-emptive administration of an NSAID could delay renal clearance of OSPHOS and may potentiate negative renal effects. Dechra recommends that NSAID therapy should be discontinued before and after dosing with OSPHOS.

13. What should be done if horse has an adverse reaction following OSPHOS® (clodronate injection) administration?

Dechra recommends monitoring horses for 2 hours following the administration of OSPHOS. If a horse appears uncomfortable, nervous, or experiences cramping posttreatment Dechra advises to hand-walk the horse until signs resolve. Owners should be advised to contact their veterinarian if the horse displays abnormal clinical signs. To report an adverse reaction, or to obtain a copy of the SDS for OSPHOS contact

Dechra Veterinary Products at (866) 933-2472 or support@dechra.com. For more information and complete product information, visit www.dechra-us.com or www.osphos.com.

Brief summary:

As with all drugs, side effects may occur. The most common adverse reactions reported in the field study were clinical signs of discomfort or nervousness, colic and/or pawing. Other signs reported were: lip licking, yawning, head shaking, injection site swelling, and hives/pruritus. Osphos should not be used in pregnant or lactating mares, or mares intended for breeding. 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.osphos.com.

OSPHOS®
(clodronate injection)

Bisphosphonate

CAUTION: Federal law (USA) restricts this drug to use by or on the order of a licensed veterinarian.
For intramuscular use in horses only.

DESCRIPTION: Clodronate disodium is a non-amino, chloro-containing bisphosphonate. Chemically, clodronate disodium is (dichloromethylene) diphosphonic acid disodium salt and is manufactured from the tetrahydrate form.

The structural formula of clodronate disodium is: Molecular Formula: CH2CL2O6 P2.2Na Molecular Weight: 288.85

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

INDICATION: For the control of clinical signs associated with navicular syndrome in horses.

DOSAGE AND ADMINISTRATION: Administer 1.8 mg/kg by intramuscular injection up to a maximum dose of 900 mg per horse. Divide the total volume evenly into three separate injection sites. Discard 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). Of the horses that responded to treatment with OSPHOS in the field study, 65% maintained their level of improvement through the 6 month evaluation.

If there is no response to initial therapy, the horse should be re-evaluated. For horses that initially respond to OSPHOS but do not maintain their clinical improvement for 6 months, OSPHOS may be re-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 recur.

CONTRAINDICATIONS: Horses with hypersensitivity to clodronate disodium should not receive OSPHOS.

WARNINGS: Do not use in horses intended for human consumption.

Human Warnings: Not for human use. Keep this and all drugs out of the reach of children. Consult a physician in case of accidental human exposure.

PRECAUTIONS: As a class, bisphosphonates may be associated with gastrointestinal and renal toxicity. Sensitivity to drug associated adverse reactions varies with the individual patient. Renal and gastrointestinal adverse reactions may be associated with plasma concentrations of the drug. Bisphosphonates are excreted by the kidney; therefore, conditions causing renal impairment may increase plasma bisphosphonate concentrations resulting in an increased risk for adverse reactions. Concurrent administration of other potentially nephrotoxic drugs should be approached with caution and renal function should be monitored. Use of bisphosphonates in patients with conditions or diseases affecting renal function is not recommended. Administration of bisphosphonates has been associated with abdominal pain (colic), discomfort, and agitation in horses. Clinical signs usually occur shortly after drug administration and may be associated with alterations in intestinal motility. In horses treated with OSPHOS these clinical signs usually began within 2 hours of treatment. Horses should be monitored for at least 2 hours following administration of OSPHOS.

Bisphosphonates affect plasma concentrations of some minerals and electrolytes such as calcium, magnesium and potassium, immediately post-treatment, with effects lasting up to several hours. Caution should be used when administering bisphosphonates to horses with conditions affecting mineral or electrolyte homeostasis (e.g. hyperkalemic periodic paralysis, hypocalcemia, etc.).

The safe use of OSPHOS has not been evaluated in horses less than 4 years of age. The effect of bisphosphonates on the skeleton of growing horses has not been studied; however, bisphosphonates inhibit osteoclast activity which impacts bone turnover and may affect bone growth.

Bisphosphonates should not be used in pregnant or lactating mares, or mares intended for breeding. The safe use of OSPHOS has not been evaluated in breeding horses or pregnant or lactating mares. Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of months to years. The 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 abnormalities in the fetus. 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 control) of various breeds, 4 to 22 years of age, and weighing 807 to 1,322 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 hives required treatment with flunixin and dexamethasone 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

CLINICAL SIGN	OSPHOS (n=111)	Control (n=35)
Uncomfortable, Nervous, Colic, and/or Pawing	9.0% (10)	0% (0)
Lip licking	5.4% (6)	0% (0)
Yawning	4.5% (5)	0% (0)
Head shaking	2.7% (3)	0% (0)
Injection site swelling	1.8% (2)	2.9% (1)
Colic requiring treatment*	0.9% (1)	0% (0)
Hives/Pruritus	0.9% (1)	0% (0)

* This horse experienced colic and hives and recovered after treatment with flunixin and dexamethasone.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Dechra at (866) 933-2472. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

INFORMATION FOR HORSE OWNERS: Owners should be advised to observe their horse for at least 2 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 hand walk the horse for 15 minutes until signs resolve. Owners should be advised to contact their veterinarian if the horse displays abnormal clinical signs.

CLINICAL PHARMACOLOGY: Clodronate disodium is a non-nitrogen containing bisphosphonate that inhibits bone resorption by binding to calcium phosphate crystals (inhibiting their formation and dissolution), and by exerting direct cellular effects on osteoclasts (inhibiting osteoclast cell function)[1]. Bound to bone matrix, clodronate disodium enters resorbing osteoclasts, alters their morphology and reduces the number of active osteoclasts, regardless of the cause of osteoclast activity[2,3].

In humans, 60 to 80% of clodronate disodium administered intravenously is eliminated unchanged in the urine and 5% in the feces[2]; the remainder of the administered dose is distributed to bone. The bone residence time in horses could not be estimated. However, in numerous studies, the half-life of clodronate disodium in rodent bone (long bones and lumbar vertebrae) has been estimated to be months to years.

After intramuscular injection, clodronate disodium is rapidly absorbed and cleared from the plasma. Within a dosing range of 1.8 to 5.4 mg/kg (n=8 per dose group), the C_{max} values increased in proportion to the dose. However, dose related changes were observed after the third administration of a regimen consisting of a single 5.4 mg/kg intramuscular injection administered once every 28 days. In this 3X dose group, a decrease in apparent total systemic clearance (CL/F) was seen (0.08 mL/hr + 0.02; mean + standard deviation), resulting in a greater than proportional increase in systemic drug exposure (AUC, 62.49 hr*mcg/mL ± 18.52) and plasma elimination T ½ (2.89 hours ± 1.33). In comparison, the estimated mean CL/F in horses receiving the 1X (1.8 mg/kg) dose was 0.12 mL/hr + 0.02 (mean + standard deviation) and the corresponding mean pharmacokinetic parameters were 5.36 ± 0.98 mcg/mL (C_{max}), 12.15 ± 1.83 hr*mcg/mL (AUC),1.65 ± 0.52 hours (T ½) and 20 minutes (T_{max}).

EFFECTIVENESS: A double masked 3:1 randomized, negative control, multi-site field study evaluated the effectiveness of a single dose of 1.4 mg/kg OSPHOS (maximum dose of 900 mg/horse) for the control of clinical signs associated with navicular syndrome in horses. Enrolled horses had a unilateral or bilateral forelimb lameness of Grade ≥ 2 on the AAEP lameness scale (Grade 0 to 5) and a diagnosis of navicular syndrome based on lameness exam, diagnostic nerve blocks, and radiographic signs indicative of the bony changes associated with navicular syndrome. Horses with radiographic signs indicating concurrent soft tissue injury, osteoarthritis, fractures, or any condition other than the bony changes related to navicular syndrome were not eligible for enrollment. 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. Lameness scores were also recorded on Day 28 and Day 180.

Of the 211 horses screened for enrollment, 146 horses received treatment (111 OSPHOS and 35 saline control). 29% of horses screened for enrollment were not eligible based on radiographic findings. 114 horses (86 OSPHOS, 28 saline control) were included in the statistical analysis. Effectiveness was evaluated on Day 56 post-treatment. On Day 56, 68 of the 86 OSPHOS treated horses and 1 out of 28 saline treated horses were treatment successes. Based on the statistical analysis, the estimated least squares mean success rates are 74.7% and 3.3% for the OSPHOS and saline treated groups, respectively. The difference in success rates is significant at P=0.0028.

Table 2: Day 56 Treatment Success Rate

Study Day	OSPHOS	Saline	P Value*
56	74.7%	3.3%	0.0028

* P value and estimated success rates are based on back-transformed mean estimates from the statistical analysis.

Treatment success based on Day 28 and Day 180 lameness scores was also assessed but not statistically analyzed. At Day 28, 67.4% (60/89) OSPHOS treated horses were considered successes, compared to 20.7% (6/29) in the saline treated group. Day 56 treatment successes were followed to the Day 180 assessment, and Day 56 treatment failures were also considered failures at Day 180. Of the 68 OSPHOS treated horses that were deemed treatment successes on Day 56, 60 were evaluable at Day 180. Of these 60 horses, 51 remained treatment successes at Day 180 based on improvement in lameness grade as compared to Day 0. However, 21 of these 60 evaluable horses demonstrated an increase in lameness grade at Day 180 as compared to their Day 56 evaluation. Including the 18 treatment failures at Day 56, the estimated overall success rate for OSPHOS at Day 180 is 65.4% (51/78).

Table 3: Day 28 and Day 180 Treatment Success Rates

Study Day	OSPHOS	Saline
28	67.4% (60/89)	20.7% (6/29)
180	65.4% (51/78)*	None evaluable

* The 18 horses that were treatment failures on Day 56 were considered to remain treatment failures at Day 180. No Day 180 lameness evaluation was performed on these horses. 60 horses (all OSPHOS treated horses) completed the Day 180 lameness evaluation.

ANIMAL SAFETY: Two studies were conducted to assess the safety of OSPHOS in horses, a six month target animal safety (TAS) study and a two phase study evaluating the safety of concurrent use of the recommended dose of OSPHOS with an NSAID and a single 5X (9 mg/kg) dose of OSPHOS.

Target Animal Safety Study: In the TAS study, OSPHOS was administered to 32 healthy adult horses at 0, 1.8, 3.6 and 5.4 mg/kg (0, 1, 2, and 3X the recommended dose) every 28 days for 6 consecutive months. OSPHOS was administered by intramuscular injection with the total volume divided evenly into at least three separate injection sites with a maximum of 15 mL per injection site.

In the TAS study, the most common post-treatment observations were clinical signs related to abdominal discomfort (colic) and the central nervous system. The incidence of colic was dose related. In the TAS study, colic was observed following 94% (45/48) of 3X treatment administrations, 54% (26/48) of 2X treatment administrations, 4% (2/48) of 1X treatment administrations, and 8% (4/48) of 0X treatment administrations. 80% (36/45) of the 3X horses, 31% (8/26) of 2X horses and none of the 1X (0/2) and 0X (0/4) horses required hand walking to relieve clinical signs associated with colic. In the 3X group, clinical signs of colic often persisted after hand walking and horses were often walked more than once. Colic related clinical signs began shortly after administration (ranging from 1 to 227 minutes post-treatment). No horses in any treatment group received medical treatment and all horses returned to normal within 5.5 hours post-treatment.

In the TAS study, post-treatment clinical signs also included yawning, flehmen, tongue rolling, head shaking and neck writhing. The signs were observed in 50% (4/8) of 0X, 100% (8/8) of 1X, 88% (7/8) of 2X, and 100% (8/8) of 3X horses. All horses returned to normal within 5.5 hours post-treatment.

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

	Number of Observations per Treatment Group (N=48 treatment administrations per group)			
Clinical Sign	**0X**	**1X**	**2X**	**3X**
Colic*	4	2	26	45
Colic requiring hand walking	0	0	8	36
Yawning	5	17	16	30
Flehmen	0	0	8	2
Tongue rolling	1	10	8	10
Head shaking	1	5	3	7
Neck writhing	0	0	0	6
Pawing	4	4	12	23
Agitation	1	1	7	10
Depression	0	2	5	21
Muscle fasciculations/Trembling	0	0	1	4

* 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 0.9-1.9 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. Individual animal potassium concentrations were within the reference range with the exception of two 3X 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, creatine 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.

NSAID and 5X 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 (5X) 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 nervousness including pawing, circling, and tail twitching within 6 minutes of dosing. Four of six horses also developed clinical signs including excessive yawning, flehmen, 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 0.9-1.9 mg/dL) for 12 hours post-treatment.

STORAGE INFORMATION: Store at controlled room temperature 25ºC (77ºF) with excursions between 15ºC-30ºC (59ºF-86ºF) 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 (60 mg/mL) per vial. NDC 17033-460-15

DISTRIBUTED BY:
Dechra Veterinary Products
7015 College Boulevard, Suite 525,
Overland Park, KS 66211 USA
For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Dechra Veterinary Products at (866) 933-2472.

Manufactured in Canada.

NADA 141-427, Approved by FDA

US Patent 7,781,420

TAKE TIME  OBSERVE LABEL DIRECTIONS

[1] Fleisch H. 1987. Bisphosphonates-history and experimental basis. Bone 8: S23-28.
[2] Plosker GL, Goa KL. 1994. Clodronate. A review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. Drugs 47: 945-982.
[3] Flanagan AM, Chambers TJ. 1989. Dichloromethylene bisphosphonate (Cl2MBP) inhibits bone resorption through injury to osteoclasts that resorb Cl2MBP-coated bone. Bone Miner: 6:33-43.

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