

**IPAR**



## **Publicly Available Assessment Report for a Veterinary Medicinal Product**

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Osphos 51 mg/ml solution for injection for horses

**PRODUCT SUMMARY**

<b>EU Procedure Number</b>	IE/V/0508/001 (formerly UK/V/0554/001)
<b>Name, Strength, Pharmaceutical Form</b>	Osphos 51 mg/ml solution for injection for horses
<b>Active Substances(s)</b>	Clodronic acid
<b>Applicant</b>	Dechra Regulatory B.V., Handelsweg 25, 5531 AE Bladel, Netherlands
<b>Legal Basis of Application</b>	Full application (Article 12(3) of Directive No 2001/82/EC)
<b>Target Species</b>	Horses
<b>Indication For Use</b>	For the alleviation of clinical forelimb lameness associated with the bone resorptive processes of the distal sesamoid (navicular bone) in adult horses.
<b>ATC Code</b>	QM05BA02
<b>Date of completion of the original decentralised procedure</b>	20 May 2015 (UK) 03 September 2015 (IE)
<b>Date product first authorised in the Reference Member State (MRP only)</b>	N/A
<b>Concerned Member States</b>	Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Luxembourg, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden

**PUBLIC ASSESSMENT REPORT**

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

## **I. SCIENTIFIC OVERVIEW**

Osphos 51 mg/ml Solution for Injection for Horses contains the active substance disodium clodronate, which belongs to the bisphosphonate class of compounds, and has the ability to decrease bone resorption. Disodium clodronate is currently authorised for both oral and intravenous use in human medicine for the treatment of conditions including osteoporosis, Paget's disease of bone, and malignant neoplasms of the bone.

Osphos is authorised for use in horses of 4 years of age or older for the control of clinical signs associated with the bone resorptive process of navicular syndrome. Navicular syndrome is a common cause of intermittent forelimb lameness that can affect horses of all activity groups. It is a poorly understood, incurable, degenerative condition of distal sesamoid (navicular) bone and supporting soft tissue structures. As navicular syndrome is associated with bone resorption treatment with a drug that inhibits bone resorption may be of benefit.

The product is given by intramuscular (IM) injection and the amount administered is 1.80 mg disodium clodronate (1.53 mg clodronic acid) per kg bodyweight, corresponding to 3 ml per 100 kg bodyweight. Osphos 51 mg/ml Solution for Injection should not be administered intravenously or used in horses with renal insufficiency. Refer to the Summary of Products Characteristics (SPC) for full detail. Horses are considered minor species; therefore this is considered a minor use minor species (MUMS) application.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

## **II. QUALITY ASPECTS**

### ***II.A. Composition***

The product contains the active substance disodium clodronate as clodronic acid and the excipients sodium hydroxide and water for injections.

The container/closure system consists of a clear Type I glass vial, closed with a chlorobutyl rubber stopper, aluminium seal and plastic flip-off cap. Each vial is then packaged in a cardboard carton. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

### ***II.B. Description of the Manufacturing Method***

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by the solubilisation of the active substance in water for injections, with adjustment of the pH. Vials are filled in a nitrogen environment. Process validation data on the product have been presented in accordance with the relevant European guidelines.

### ***II.C. Control of Starting Materials***

The active substance, disodium clodronate is described in the European Pharmacopoeia. Data on the active substance were supplied in the form of an Active Substance Master File (ASMF) from the manufacturer. The active substance is manufactured in accordance with the principals of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Excipients comply with the relevant Ph. Eur. monographs and batch analysis has been provided.

#### ***II.C.4. Substances of Biological Origin***

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

#### **II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process**

Not applicable.

#### **II.E. Control Tests on the Finished Product**

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The tests include those for identification and assay of the active substance, identification of impurities, appearance, pH and sterility.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

#### **II.F. Stability**

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 5 years has been determined.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data were provided for batches stored at 30°C/65% RH for 12 months and at 40°C/75% RH for 6 months. A shelf life of 2 years was established. Further stability data in accordance with the relevant guidelines have been provided supporting an extended shelf of the finished product of 3 years.

#### **G. Other Information**

##### Shelf life

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

##### Special precautions for storage

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

### III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

#### III.A Safety Documentation

##### Pharmacological Studies

##### Pharmacodynamics

Clodronic acid is a bisphosphonate and a potent inhibitor of osteoclast[1]-mediated bone resorption. It is extensively used in human medicine to treat various diseases associated with increased bone resorption.

The primary target of clodronate is the osteoclasts, with clodronic acid being seen to act directly on osteoclasts both in vitro and in vivo. Clodronic acid enters the osteoclast and alters the morphology, reducing the number of active osteoclasts. Clodronic acid also inhibits the dissolution of hydroxyapatite crystals as a result of physicochemical interactions with calcium. Clodronic acid has a high affinity for solid-phase calcium phosphate which causes it to accumulate in bone and inhibit the formation, aggregation and dissolution of calcium phosphate crystals.

The effect of disodium clodronate on bone mineral density (BMD) has been investigated in vivo and several studies were cited in support of the application. In studies ovariectomised rats received clodronate doses of 100 – 500 mg/kg bw orally or 4 – 25 mg/kg bw via subcutaneous (SC)/ intraperitoneal (IP) injection daily for 3 days to 12 weeks. In a further study osteopenia-induced rats received 3 – 25 mg/kg bw of clodronate via SC injection for 3 or 6 months. The results of both studies demonstrated that clodronate decreased the total loss of BMD and the trabecular loss of BMD. Clodronate was able to prevent the weakening of bone and suppress osteopenia in oestrogen-deficient rats.

Similar studies in healthy rats indicated that clodronate (2 – 12 mg/kg bw SC, once or twice a week for 6 months) increased the bone mass, trabecular bone area and the maximum load in compression tests. The excretion of calcium and the concentration of osteocalcin[2] decreased. Studies in animals with fractures indicate clodronic acid may retard bone remodelling, and in rat arthritis models clodronate appeared to suppress the intensity of the inflammation as well as secondary articular and bone lesions.

##### Pharmacokinetics

Clodronate is poorly absorbed following oral administration with a very low bioavailability (<5%) in rats and humans. However bioavailability and absorption are much greater following intramuscular or subcutaneous injection. In a pharmacokinetic study in horses, the maximum plasma concentration (7.5 µg/ml) was reached in 35 minutes following administration of 900 mg disodium clodronate (765 mg clodronic acid) by IM injection.

In studies conducted in rats and mini-pigs no metabolites of disodium clodronate were detected. This indicates that clodronate is not metabolised. This is expected as clodronate is a bisphosphonate, a synthetic compound, which is not biodegradable or hydrolysable in solution.

Distribution studies in rats and mice showed clodronate is rapidly distributed to the target tissue, bone, with relatively high levels detected even 12 months after administration. The studies indicate that the incorporation of clodronate into bone is greatest in areas with the highest bone remodelling rate. The route of administration (intravenous [IV], IP or SC) had no effect on clodronate deposition.

In rats, following oral administration, clodronate is mainly excreted via faeces, due to its low bioavailability. Following IV, IM or SC injection clodronate is mainly excreted in the urine (>53%) with a plasma half-life of 1-2 hours regardless of the administration route. In horses the elimination plasma half-life is 5.6 hours but the overall pharmacokinetic profile is comparable. A slight difference has been observed between male and female horses with a slightly higher AUC[3], C<sub>max</sub>[4], half-life and T<sub>max</sub>[5] seen in female horses compared to males following single IM administration.

### ***Toxicological Studies***

The applicant has provided information and studies to demonstrate the safety of clodronate sodium.

#### ***•Single Dose Toxicity***

Single dose toxicity studies in a number of species were provided and discussed. Studies were conducted in rat, mice and mini-pig with clodronate administered orally or via IV injection. The LD<sub>50</sub> of clodronate was 155.6 mg/kg bw for mice and 119.8 mg/kg bw for rats following IV injection and >4500 mg/kg bw and 2203 mg/kg bw for mice and rats respectively after oral administration. The LD<sub>50</sub>[6] for mini-pigs was not determined as no animals died following single administration of 150 or 300 mg/kg bw. Renal toxicity, reduction in erythrocytes and liver toxicity was observed but there were no deaths. No adverse effects were seen in mice but clinical observations were made in rats. Tremors and convulsions were seen following administration and necropsy showed the target organs were the stomach, liver and seminal vesicles.

Acute oral toxicity is considered to be low and the target organs are the liver and kidneys. Following oral administration distension of the gastrointestinal tract was observed but this was not seen after IV administration so is considered a side effect of oral exposure.

#### ***•Repeated Dose Toxicity***

Studies investigating the effect of repeat oral and IV administration in rats and mini-pigs were provided. It was noted in rats that oral administration caused a

reduction in absolute and relative liver weight and kidney weight as well as trabecular extensions in bones. The LOAEL[7] for rats was 100 mg/kg bw/day. An LOAEL of 100 mg/kg bw/day was also established for mini-pigs in one study where clodronate was orally administered for 3 months. Changes to the blood chemistry, including coagulation parameters and erythrocyte count, were observed. In a second study where mini-pigs received clodronate for 12 months, effects on the blood chemistry, gastrointestinal tract and bone were observed but the changes were completely reversed after a 4 month recovery period.

Studies were conducted for IV administration to rats and mini-pigs. The observed effects were similar to the effects following oral administration. Liver and kidney toxicity were noted and haematopoiesis was observed in both species. Osteosclerosis was observed with bone growth into the bone marrow cavity and a resulting increase in length and compactness of bone. An NOAEL[8] could not be established but effects were seen in both rats and mini-pigs at IV doses of  $\geq 1$  mg/kg bw/day.

•Reproductive Toxicity, including Teratogenicity:

Studies investigating the reproductive toxicity of clodronate were provided. In one study male and female rats received 0, 50, 200 or 600 mg/kg bw/day and 0, 50, 100 or 200 mg/kg bw/day respectively. The rats received the oral treatment throughout a 21 day cohabitation period. The effects of treatment observed in male rats included reduction in bodyweight, testes weight, epididymis weight and an increase in testicular and epididymal lesions. Reduced mating and fertility were also seen. Female rats were also seen to have a reduced bodyweight and a reduced number of corpora lutea, as well as an increased level of mortality thought to be due to an inability to deliver pups. The first generation offspring were also monitored and all offspring had a reduced fertility index.

The NOEL[9] was calculated for male rats as 50 mg/kg bw/day but for effects on reproductive performance this was higher (200 mg/kg bw/day). For females the NOEL was determined as 50 mg/kg bw/day, with reproductive effects seen at this level. The NOEL for viability and growth of first generation offspring was calculated as 100 mg/kg bw/day.

Embryotoxicity was also investigated and studies were provided. In one study using rabbits, clodronate was administered orally and maternal rabbits had reduced bodyweight and increased morbidity following treatment, with a reduced average and live litter size. The NOAEL was 70 mg/kg bw/day for maternal rabbits and 300 mg/kg bw/day for foetal effects. A similar study in rats produced an NOAEL of 50 mg/kg bw/day for maternal rats with gastric lesions, clinical signs and death observed. The foetal effect was a reduced bodyweight of the pup and an NOAEL of 100 mg/kg bw/day was calculated.



Treatment with disodium clodronate during late-stage gestation was seen to cause a reduction in serum calcium in the pregnant rats. This was considered to contribute to the late-gestational mortality in treated rats and could not be prevented with calcium supplementation. The studies showed clodronate is not teratogenic.

#### •Mutagenicity

Mutagenicity studies were performed in vitro and in vivo for disodium clodronate to test for gene mutations and chromosomal effects. Clodronate was not found to have any mutagenic effect on genes or chromosomes during tests using mouse bone marrow, human bone marrow and blood cells and Chinese hamster ovary cells. In addition a literature review was provided on clodronate use in human medicine. There is no evidence of chromosomal effects in patients with Paget's disease receiving long-term treatment with clodronate. It was concluded that disodium clodronate is not mutagenic.

#### •Carcinogenicity

Carcinogenicity studies were conducted in mice and rats following oral administration of clodronate. Administration of clodronate did not increase the mortality of mice and rats although some clinical signs were observed resulting in a NOAEL of 45 mg/kg bw/day in mice and an NOAEL was not determined for rats as effects were observed at the lowest dose, 50 mg/kg bw/day. No evidence of carcinogenicity was observed in either species and clodronate has not been found to be mutagenic.

#### ***Studies of Other Effects***

A study was conducted to investigate the vaso- and tissue irritation properties of disodium clodronate. Clodronate was administered via IV or SC injection to dogs for 5 days at either 0, 6 or 24 mg/kg bw IV or 0, 3 or 12 mg/dog SC. Animals were autopsied 3 days after the final dose and no clinical signs of vaso-irritation or tissue irritation were observed.

#### ***Observations in Humans***

Clodronate has been used in human medicine for a number of years. Many studies have been conducted to investigate the efficacy of clodronate in humans following different routes of administration and with different treatment protocols. The most common effects observed in humans following oral administration are gastrointestinal disturbances, including vomiting, nausea and diarrhoea. The effects tend to be mild and transient and can be reduced by dividing or lowering the dose. In humans clodronate is well tolerated following IV administration.

#### ***User Safety***

A user risk assessment was provided in compliance with the relevant guideline which shows that the product is expected to be administered and handled by veterinary surgeons and nurses only. The main risks of exposure are through accidental

injection or spillage onto skin. The risk of children being exposed to the product is considered negligible. The risk of exposure to the product is considered to be low. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product; as clodronate used in human medicine is contraindicated in pregnant women a suitable warning is included on the SPC and product literature.

- 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.

### ***Environmental Safety***

A Phase I environmental risk assessment (ERA) has been provided. The ERA was conducted in accordance with VICH and CVMP guidelines.

#### Phase I:

The Phase I assessment showed the product will only be used to treat a small number of individual animals. In addition, clodronate will largely be retained in the skeleton and as such environmental exposure will be low. The product is not expected to pose a risk to the environment, therefore a Phase II ERA was not required.

### ***III.B.2 Residues documentation***

#### ***Residue Studies***

A residue depletion study was provided. The study was performed in horses using the test product administered at the maximum dose split over 2 injection sites. Kidney, liver, abdominal fat and injection site muscle samples were collected at 12, 24, 48 and 96 hours after administration. The samples were analysed using LC-MS/MS and the methods were validated. The results showed that residues depleted quickly from injection site muscle and fat but clodronate persists at a low level in the liver and kidney.

#### ***MRLs***

The CVMP concluded an MRL for clodronic acid in equidae was not necessary for the protection of human health. Therefore, clodronic acid is listed in Table 1 of the Annex to Regulation 37/2010 and no MRL is required.

#### ***Withdrawal Periods***

Meat and offal: Zero days

Not authorised for use in animals producing milk for human consumption.

[1] Osteoclast – a bone cell that resorbs bone tissue

[2] Osteocalcin – a protein involved in bone mineralisation

- [3] AUC - Area Under the Curve (plasma concentration versus time curve)
- [4] Cmax – Maximum plasma concentration
- [5] Tmax – Time to maximum concentration
- [6] LD50 – The dose that kills 50% of the population
- [7] LOAEL – Lowest observed adverse effect level
- [8] NOAEL – No observed adverse effect level
- [9] NOEL – No observed effect level

## **IV. CLINICAL ASSESSMENT**

### ***IV.1. Pre-Clinical Studies***

#### ***Pharmacology***

##### Pharmacodynamics

Clodronic acid, clodronate, is a bisphosphonate and a potent inhibitor of osteoclast-mediated bone resorption. Clodronate is extensively used in human medicine to treat various diseases associated with increased bone resorption.

Bisphosphonates are synthetic molecules with a P-C-P bond which have a high affinity for calcium phosphate and bind strongly to hydroxyapatite crystals. They accumulate in mineralised tissue and are potent inhibitors of bone resorption.

Clodronate is internalised by osteoclasts and alters the morphology of the cell, reducing the number of active osteoclasts. Clodronate reduces osteoclast recruitment and causes earlier apoptosis[1] thus shortening the life span of the cell and limiting osteoclast activity. It is also thought to act indirectly on osteoclasts by triggering changes in the levels of prostaglandins, lactic acid and lysosomal enzyme activity which stimulates secretion of an inhibitor of osteoclast recruitment by osteoblast[2] cells. Clodronate also inhibits the dissolution of hydroxyapatite crystals as a result of physicochemical interactions with calcium. Clodronate inhibits the formation, aggregation and dissolution of calcium phosphate crystals thus reducing bone turnover.

In the horse, evidence suggests bone remodelling within the distal sesamoid bone is important in horses diagnosed with navicular disease. The changes observed are as a result of increased bone turnover due to increased osteoclast and osteoblast activity. In addition to the increased turnover there is an uncoupling of resorption and formation as there is excessive resorption and bone formation is often not sufficient to replace the resorbed bone. This leads to increased bone porosity and bone loss.

Clodronate inhibits periodontal bone destruction, bone changes and inflammation. Unlike more potent bisphosphonates, clodronate spares osteoblastic function which

means bone may still form. Clodronate may also alleviate pain by reducing bone resorption.

### Pharmacokinetics

Clodronate is poorly absorbed following oral administration with a very low bioavailability. This is thought to be due to the low lipophilicity and high negative charge of bisphosphonates. Following absorption 20 – 80% is taken up by bone and the remainder rapidly excreted in the urine. If large amounts are administered clodronate will be deposited in other organs, such as the liver and spleen. If administered in smaller quantities clodronate will deposit preferentially in areas of bone resorption. In humans the half-life of bisphosphonates is 0.5 – 2 hours and approximately 60 – 80% of clodronate is eliminated unchanged in the urine and 5% in the faeces. The remainder is distributed to bone.

The pharmacokinetic profile has been determined for horses. Following single intramuscular injection to horses diagnosed with navicular syndrome clodronic acid is rapidly absorbed and then eliminated more slowly. There was apparent correlation between the AUC and  $C_{max}$  and the dose administered. The AUC following IM administration of the maximum recommended dose, 900 mg disodium clodronate (765 mg clodronic acid), was 22.84 ( $\pm 3.17$ ) h/ $\mu$ g/ml and the  $C_{max}$  was 7.46 ( $\pm 1.74$ )  $\mu$ g/ml. The plasma half-life was approximately 5.62 ( $\pm 5.59$ ) hours and the maximum concentration was reached after 0.58 hours ( $T_{max}$ ).

### ***Tolerance in the Target Species***

Two controlled target animal tolerance studies were conducted using multiples of the recommended dose in the target species. As a class, bisphosphonates are associated with gastrointestinal and renal toxicity. Bisphosphonates are also known to affect the plasma concentrations of some minerals and electrolytes, such as calcium, magnesium and potassium. Therefore caution is required when administering such drugs to patients with conditions affecting mineral or electrolyte homeostasis, e.g. hypocalcaemia.

In the first target species tolerance study a suitable number of male and female horses over the age of 4 years were given the test product. The horses were given phenylbutazone treatment (4.4 mg/kg twice daily) on day 0-3 of the study then on days 4-6 this was reduced (2.2 mg/kg twice daily). On day 4 the horses received clodronate (1.8 mg/kg maximum dose 900 mg) by IM injection at 3 separate sites. Following a washout period the horses then received an overdose of clodronate (9 mg/kg maximum dose 4500 mg) administered at 5 different intramuscular sites. Horses were observed for general health and behaviour alongside more detailed clinical examinations as well as blood samples taken for analysis.

The results of the study found no clinically significant changes in the general health or behaviour of the horses and no injection site reactions were seen following administration of 1 x dose. After administration of the 5 x dose adverse reactions were seen in all the horses. The reactions observed included nervousness, central nervous system (CNS) signs such as head shaking, mild to moderate muscle fasciculations and signs of discomfort and abdominal pain. Most horses experienced moderately severe reactions that lasted 1-4 hours but one horse had a severe reaction within 8 minutes of treatment and had to be treated for colic and was not clinically normal until 7 hours after treatment. Analysis of the blood samples showed an increase in blood urea nitrogen (BUN), creatinine, GGTP[3] and creatine kinase (CPK) post-treatment compared to pre-treatment. Statistically significant changes in ionised calcium, sodium chloride and magnesium were not observed during the study. There were also no significant changes in the haematology or coagulation findings. It was concluded that the administration of the test product at 1.8 mg/kg, in conjunction with phenylbutazone treatment, is well tolerated by horses but administration of 9 mg/kg resulted in significant adverse events immediately after treatment.

A second study was conducted to determine the margin of safety of the test product in the target species. A larger number of male and female horses, of various breeds, aged 4 years or over were divided into 4 treatment groups using a randomised complete block design. Group 1 acted as control and received a placebo dose (0.9% saline), Group 2 received 1.8 mg/kg, Group 3 received a 2 x dose (3.6 mg/kg) and Group 4 were given a 3 x dose (5.4 mg/kg). Each horse received treatment via IM injection at multiple sites every 28 days for 6 treatments. Horses were observed for general health and physical examinations were made, mechanical bone testing and bone density readings were performed as well as clinical pathology sample analysis and macroscopic pathology examinations. Blood and urine samples were collected for analysis.

Injection site reactions were observed in all treatment groups, characterised by soft or firm swellings which resolved within 10 days. No clinically significant changes were noted during physical examinations but significant dose related adverse events were recorded. The majority of events were CNS or GI tract related. The clinical signs observed included yawning, Flehmen's response and head shaking as well as acute abdominal discomfort (colic signs). The most common sign was abdominal discomfort which was seen most frequently in the 3 x treatment group (incidence of colic 0x = 8%, 1x = 4%, 2x = 54%, 3x = 94%). All horses were normal within 3 hours of injection.

Statistically significant increases in BUN, creatinine and CPK were observed in the 2x and 3x groups following treatment. No significant changes were noted in the 1x group and all results had returned to normal by the end of the study. No significant changes were observed from haematology, including coagulation results, and urine

samples did not show any differences between the groups. The mean levels of ionised calcium were reduced in the 3x group but no clinically significant changes were noted for calcium, potassium or magnesium. No significant treatment effects were observed for bone density or bone strength.

It was concluded that treatment with increasing doses of disodium clodronate increases the incidence and severity of adverse reaction, predominately CNS and GI effects, but treatment with 1.8 mg/kg is well tolerated by horses. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

#### **IV.II. Clinical Documentation**

##### **Laboratory Trials**

Dose determination and confirmation studies have been provided which show that the lowest effective dose is 1.8 mg/kg bw (maximum of 900 mg/horse) disodium clodronate in horse. Studies were provided to confirm the efficacy of disodium clodronate administered at this dose and significant improvements to the clinical symptoms of navicular syndrome were seen following administration of this dose.

A field study was also conducted in horses diagnosed with navicular syndrome and meeting a set of inclusion criteria. Significant improvement was observed in the clinical condition of horses treated with the test product, Osphos, compared to horses treated with a placebo, saline solution. The study also demonstrated that the product is safe for use in horses at the confirmed dose and reported adverse reactions were mild and transient.

##### **Dose confirmation studies:**

Study title	Dose titration study of a preparation containing clodronic acid for intramuscular injection in horses suffering from navicular disease (podotrochilitis chronica aseptica)
Objectives	To determine the recommended dose and the clinical effectiveness of various dosages of the test product.
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Disodium clodronate. Group 1 – 300 mg Group 2 – 900 mg Group 3 – 1500 mg

	Each horse was administered the contents of 5 vials, with saline making up the remaining volume, via intramuscular injection at 5 separate sites.
Control product/placebo	Placebo. Group 4 – Saline 25 ml  Saline administered IM at 5 separate injection sites.
Animals	29 healthy horses aged 4-14 years with navicular disease which had not been treated with NSAIDs or steroids within 30 days of the start of the study.  Navicular disease was diagnosed as follows: <ul style="list-style-type: none"> <li>• Slight to moderate, possibly intermittent, foreleg lameness (one or both sides)</li> <li>• Pain when turning (one or both sides)</li> <li>• Clearly positive anaesthesia of the distal palmar digital nerves possibly with lameness reversal.</li> <li>• Radiographic changes in the form of an increased number (<math>\geq 5</math>) of sesamoidal canals on the distal edge of the navicular bone</li> <li>• Expanded sesamoidal canals on the distal edge of the navicular bone, possibly lollipop shaped areas, number branched, form of sclerosis.</li> </ul>
Outcomes/endpoints	Radiographs were taken to be reviewed for: <ul style="list-style-type: none"> <li>• Number of widened sesamoid canals</li> </ul>

	<ul style="list-style-type: none"> <li>• Number of sesamoid canals with lollipop shaped areas</li> <li>• Number appearing branched</li> <li>• Form of sclerosis</li> </ul> <p>Horses were assessed for the degree of clinical improvement:</p> <ul style="list-style-type: none"> <li>• supporting leg lameness at a walk (yes or no)</li> <li>• pain when turning (yes or no)</li> <li>• efficacy of anaesthesia of the distal palmar digital nerves</li> <li>• therapy failure defined as removed from study at Day 28 (yes or no)</li> </ul> <p>The degree of clinical improvement was determined.</p> <p>General and local tolerance was also measured.</p>
Randomisation	Randomised.
Blinding	Double blind.
Method	<p>On Day 1 horses underwent clinical and radiographic examination prior to injection of the test medication. Observation for general health and local tolerance were made for 30 minutes and at regular time points until 72 hours post-injection.</p> <p>On Day 28 and Day 183 post-treatment clinical and radiographic examination was repeated.</p>
Statistical method	<p>A Fishers exact test was used to compare the primary criteria (degree of clinical improvement) between the groups. The p value was set at &lt;0.05.</p> <p>An ANOVA was used to compare the secondary criteria with the p value &lt;0.10.</p>
RESULTS	



Outcomes for endpoints	<p>The results showed a superior clinical improvement in animals treated with 900 mg and 1500 mg of the product. Failure of therapy occurred in 9% and 0% of horses in the 900 mg and 1500 mg groups respectively and in 100% of the placebo group. The 300 mg group was not significantly different to the placebo group (<math>p &gt; 0.05</math>) and the 900 mg group was not different to the 1500 mg group (<math>p &gt; 0.10</math>). The 900 mg group was significantly better than the placebo group (<math>p &lt; 0.0001</math>).</p> <p>The radiographs showed the affected legs of the 900 mg and 1500 mg treated horses remained stable up to 6 months after treatment. There were no significant changes to any secondary endpoints (temperature, heart rate, respiration) and none of the outcomes were affected by the dose (<math>p &gt; 0.10</math>). No irritation at any of the injection sites was reported.</p>
DISCUSSION	The 900 mg dose of clodronic acid was found to be the lowest reliably effective dose.

Study title	Dose confirmation study of a preparation containing clodronic acid for intramuscular injection in horses suffering from navicular disease (podotrochilitis chronic aseptica).
Objectives	To confirm the clinical efficacy of 900 mg disodium clodronate compared to a placebo.
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	<p>Disodium clodronate  Test group (12 horses) – 900 mg disodium clodronate</p> <p>Administered by IM injection at 3</p>

	separate sites.
Control product/placebo	<p>Placebo. Control group (11 horses) – isotonic saline solution</p> <p>Administered by IM injection at 3 separate sites.</p>
Animals	<p>23 healthy horses aged 4-14 years of mixed warmblood breeds and comprising stallions, mares and geldings. The horses that were included were not treated with NSAIDs or steroids in the 30 days prior to the study.</p> <p>Horses included showed:</p> <ul style="list-style-type: none"> <li>· shuffling gait/stumbling but not assigned to a specific limb (evaluated when walking and trotting)</li> <li>· Head rocking or asymmetrical motion of the croup scarcely noticeable; repeated walking and trotting of the horse necessary to identify the lameness.</li> <li>· Mild to moderate possible intermittent lameness in a supporting leg (unilaterally or bilaterally)</li> <li>· Pain on turning (unilateral or bilateral)</li> <li>· Marked positive anaesthesia of the distal palmar digital nerves (palmar digital nerve block) (lameness has switched to the other leg)</li> <li>· Radiographic changes in the form of an elevated number (<math>\geq 5</math>) of sesamoidal canals at the distal border of the navicular bone measured in both forelimbs)</li> <li>· Widened sesamoidal canals at the distal border of the navicular bone, possibly lollipop shaped areas either branched or not.</li> </ul> <p>If any concurrent treatment was required or a serious adverse event occurred the horse would be removed from the study.</p>

Outcomes/endpoints	<p>Radiographs were taken to be reviewed for:</p> <ul style="list-style-type: none"> <li>• Number of widened sesamoid canals</li> <li>• Number of sesamoid canals with lollipop shaped areas</li> <li>• Number appearing branched</li> <li>• Form of sclerosis</li> </ul> <p>Horses were assessed for the degree of clinical effectiveness:</p> <ul style="list-style-type: none"> <li>• Lameness at trot (yes or no)</li> <li>• supporting leg lameness at a trot (yes or no)</li> <li>• pain when turning (yes or no)</li> <li>• therapy failure defined as removed from study at Day 28 (yes or no)</li> </ul> <p>The degree of clinical effectiveness was determined.</p> <p>Systemic and local tolerance was also measured.</p>
Randomisation	Randomised.
Blinding	Double blind.
Method	<p>On Day 1 horses underwent clinical and radiographic examination prior to injection of the test medication. Observation for general health and local tolerance were made for 30 minutes and at regular time points until 72 hours post-injection.</p> <p>On Day 28 and Day 183 post-treatment clinical and radiographic examination was repeated.</p>
Statistical method	A Fishers exact test was used to compare the primary criteria (degree of clinical effectiveness) between the groups. The p value was set at <0.05.

	An ANOVA was used to compare the secondary criteria with the p value <0.10.
RESULTS	
Outcomes for endpoints	<p>The results of the study showed a significant clinical improvement in horses treated with 900 mg disodium clodronate compared to those treated with the placebo. For each of the 4 clinical effectiveness criteria a significant improvement was seen in treated horses compared to untreated horses.</p> <p>On Day 28 for the treated group lameness in trot was 16.7% and for the control group was 100% (<math>p &lt; 0.0001</math>). Supporting leg lameness was 100% for the control group and was significantly lower for treated horses, 8.3% (<math>p &lt; 0.0001</math>). Pain when turning was also 100% for control horses but 25% for treated horses (<math>p = 0.0028</math>). Finally failure of therapy was 100% in the horses given the placebo and 16.7% in horses given 900 mg clodronic acid (<math>p &lt; 0.0001</math>).</p> <p>The radiographs showed the affected legs of the treated horses remained stable up to 6 months after treatment. There were no significant changes to any secondary endpoints (temperature, pulse, respiration) (<math>p &gt; 0.10</math>). No adverse reactions or irritation at any of the injection sites were reported.</p>
DISCUSSION	Rapid clinical improvement was seen in the horses administered 900 mg disodium clodronate compared to horses given a placebo. The clinical signs of navicular disease disappeared in almost all treated horses and the improvement lasted for 6 months in most horses. No deterioration in navicular bone pathology was observed in any of the treated

	horses 6 months after treatment.
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**Field Trials**

Study title	An evaluation of the clinical efficacy of clodronic acid for the control of the clinical signs associated with navicular syndrome in horses.
Objectives	To evaluate the effectiveness of disodium clodronate in controlling the clinical signs associated with navicular syndrome; to assess the clinical safety of the product.
Test site(s)	Multi-centre, veterinary practices, EU and third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Disodium clodronate. Test group – 1.4 mg/kg disodium clodronate up to a maximum of 900 mg.  Administered via IM injection at 3 separate injection sites.
Control product/placebo	Placebo. Control group - 0.9% saline equivalent volume up to a maximum of 15 ml.  Administered via IM injection at 3 separate injection sites.
Animals	146 healthy horses, aged 4-22 years of mixed breeds and comprising geldings, mares and stallions. The horses that were included were not treated with NSAIDs in the 7 days prior to the study or steroids 30 days before the study.  Exclusion criteria: <ul style="list-style-type: none"> <li>• Hind limb lameness</li> <li>• Change in shoeing pattern within 2 weeks of the first visit</li> <li>• Neurectomy</li> <li>• Radiographic signs indicative of lameness due to primary soft tissue injury, osteoarthritis, fractures or any condition</li> </ul>

	<p>other than bony changes related to navicular syndrome</p> <ul style="list-style-type: none"> <li>• Pregnant or lactating.</li> </ul> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• Forelimb lameness <math>\geq</math> grade 2 (on the AAEP[4] lameness scale).</li> <li>• Lameness, unilateral or bilateral, attributed to navicular syndrome following nerve blocks and radiographs.</li> </ul> <p>The shoeing pattern of horses had to remain unchanged throughout the study.</p>
Outcomes/endpoints	<p>The primary outcome was the clinical effectiveness. This was judged by improvement of lameness in the primarily affected limb by at least 1 AAEP lameness grade and no worsening of lameness grade due to navicular syndrome in the least lame forelimb. The % horses with an improved lameness evaluation relative to baseline was determined and expressed as % improved.</p> <p>Secondary outcomes were also measured. These included haematology, serum chemistry and physical examination.</p>
Randomisation	Horses were randomised to treatment groups in a 3:1 ratio of clodronic acid to saline control.
Blinding	Double blind
Method	Horses were assessed for lameness and radiographs were taken Days -7 to -1 to determine eligibility for enrolment and determine baseline lameness scores. On Day 0 horses received treatment with

	<p>either disodium clodronate or the placebo.</p> <p>On Days 28 and 56 horses were reassessed for lameness and blood samples were taken alongside owner interviews.</p> <p>On Day 180 owner interviews were conducted, lameness was assessed and radiographs taken. Any horses that were classed as treatment failures underwent safety observations and were offered a disodium clodronate treatment.</p> <p>At Day 240 further interviews were held with owners and horses underwent safety observations.</p>
Statistical method	<p>The primary endpoint was the improvement of lameness, % improved and 95% confidence intervals (CI) were calculated. A GLIMMIX procedure in SAS was used to compare the control and treatment groups.</p> <p>The secondary outcomes were evaluated using a repeated measure ANOVA and p value was set at 0.10.</p>
<b>RESULTS</b>	
Participant flow	<p>146 horses were enrolled in the study and 114 remained eligible for clinical effectiveness evaluation after Day 56 (test group n = 86, control group n = 28).</p> <p>By Day 180 a further 7 horses were excluded from the treatment group and 1 horse from the control group.</p> <p>Radiographs were taken at Day 180 for horses judged a treatment success on Day 56. All treatment success horses were from the treatment group (n = 61).</p>
Duration of follow-up	<p>Horses received treatment on Day 0 and follow-up assessments took place on Day 28 and 56 for all horses. Horses that responded successfully to treatment were assessed again on Day 180 whilst all</p>

	<p>other horses were evaluated for safety on Day 180. Successful cases were then observed for safety in a final follow-up on Day 180.</p>
<p>Outcomes for endpoints</p>	<p>The primary endpoint was the improvement in lameness scores. The horses in the treatment group had significantly improved scores compared to the control group. Most horses were enrolled with a lameness score of 3 or 2, which had improved to 2, 1 or 0 by Day 56. The treatment success rate was calculated for treated and control horses on Day 56. For treated horses the success rate was 74.72% (95% CI = 34.54, 94.30) and for control horses was 3.30% (95% CI = 0.34, 25.54). This was shown to be significantly different (<math>p = 0.0028</math>).</p> <p>On Day 28 a treatment success of 67.4% (95% CI = 57.68, 77.15) compared to the control group 20.69% (95% CI = 5.95, 35.43) and by Day 180 a treatment success rate of 83.61% (95% CI = 74.32, 92.90) was determined for treated horses. Radiographs were also taken on Day 180 and showed an improvement of the disease state in 3 horses and no change in the other 58 horses.</p> <p>The results for the secondary outcomes showed there were no significant treatment effects for haematology or systemic effects (<math>p &gt; 0.10</math>).</p>
<p>Adverse events</p>	<p>All adverse events that occurred were reported as being mild and transient. Following administration of the test product 9% of horses experienced mild colic and appeared uncomfortable. This was the most common adverse reaction.</p> <p>Other common adverse reactions after administration of disodium clodronate included lip licking (5.4%), yawning (4.5%)</p>



	<p>and head shaking (2.7%). Injection site swelling occurred following administration of both the test product (1.8%) and the placebo (2.9%).</p> <p>More uncommon adverse reactions that were observed following clodronic acid injection were colic requiring treatment (0.9%) and hives/pruritis (0.9%).</p> <p>The adverse events occurred between Day 0 and Day 56 of the study following observations by the vet or owner. Further clinical signs were reported for 34 horses between Day 56 and Day 240 but these were not considered to be related to treatment.</p> <p>Medications were administered concurrently to some horses during the study. These included vaccinations, dewormers, detomidine, neutraceuticals, hyaluronic acid and phenylbutazone. No apparent interactions were observed with any of these medications.</p>
DISCUSSION	<p>The results of the study showed that injection of disodium clodronate at 1.4 mg/kg alleviates the symptoms of navicular syndrome for up to 6 months with little or no additional treatment. The product was also shown to be safe and no clinically significant changes were seen in the haematology or blood biochemistry. Although adverse reaction were seen in horses receiving the test product they were mild and transient, requiring little intervention or treatment.</p>

[1] Apoptosis – programmed cell death

[2] Osteoblast – a cell that makes bone

[3] GGTP – Gamma-glutamyl transpeptidase

[4] AAEP – American Association of Equine Practitioners

## **V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT**

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable