Date of Approval: January 11, 2015

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-418

BETAVET

Betamethasone sodium phosphate and betamethasone acetate

Injectable Suspension

Horses

For the control of pain and inflammation associated with osteoarthritis

Sponsored by:

Luitpold Pharmaceuticals, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-418

B. Sponsor

Luitpold Pharmaceuticals, Inc.
Animal Health Division
Shirley, NY 11967

Drug Labeler Code: 010797

C. Proprietary Name

BETAVET

D. Established Name

Betamethasone sodium phosphate and betamethasone acetate

E. Pharmacological Category

Glucocorticoid

F. Dosage Form

Injectable suspension

G. Amount of Active Ingredient

6 mg/mL as 3.15 mg betamethasone sodium phosphate and 2.85 mg betamethasone acetate

H. How Supplied

One 5 mL vial containing 30 mg betamethasone

I. Dispensing Status

Rx

J. Dosage Regimen

9 mg (1.5 mL) per joint, for a maximum of two joints

K. Route of Administration

Intra-articular injection

L. Species/Class

Horses

M. Indication

For the control of pain and inflammation associated with osteoarthritis in horses

II. EFFECTIVENESS

A. Dosage Characterization

The dose of BETAVET selected for evaluation in the field study to support substantial evidence of effectiveness was based on available published literature and known current use patterns of betamethasone administered intra-articularly in horses. One published study evaluated the effectiveness of another betamethasone formulation for intra-articular administration in horses with arthritis[1]. Volumes administered in that study ranged from 1.5 mL to 10 mL per joint, roughly equivalent to 21 to 138 mg betamethasone per joint. A survey of American Association of Equine Practitioner (AAEP) member veterinarians noted the largest percentage (35.4%) of veterinarians who administer betamethasone intra-articularly use 6 mg to 12 mg betamethasone per joint[2]. A dose of 9 mg total betamethasone per joint (1.5 mL BETAVET) was selected to be confirmed in the field study to support substantial evidence of effectiveness.

B. Substantial Evidence

1. Clinical Field Study:

   a. Title: A pivotal multi-site clinical field trial to assess the efficacy and safety of BETAVET™ I.A. administered once intra-articularly for the improvement of clinical lameness scores in horses with lameness associated with osteoarthritis. Study number: AH-2011-001.

   b. Investigators: 18 investigators participated in the multi-site field study. Table 1 lists the investigators (16) for sites included in the statistical analysis.

Table 1. Investigators

Investigator	Location
Douglas Anez, DVM	Exeter, CA
James Beckman, DVM	Prospect, KY
Christopher Johnson, DVM	Versailles, KY
Wayne Browning, DVM	Redwood City, CA
Brian Burks, DVM	Apollo, PA
Kyle Drake, DVM	Arthur, IL
Tim Eastman, DVM	Salinas, CA
Laura Werner, DVM	Lexington, KY
J. Andy Gardner, DVM	Salisbury, NC
Gary White, DVM	Sallisaw, OK

[1] Van Pelt RW, Tillotson PJ, and Gertsen KE. Intra-articular injection of betamethasone in arthritis in horses. J Am Vet Med Assoc. 1970;156(11):1589-99.
[2] Ferris DJ, Frisbie DD, McIIwraith CW. Current joint therapies in equine practice: A survey of veterinarians. Proceedings of the 55th Annual convention of the American Association of Equine Practitioners, pages 57-58 and the Confidential Survey, pages 1-24. 05-09 December 2009. Las Vegas, Nevada.

Investigator	Location
K. Leann Kuebelbeck, DVM	Brandon, FL
Joseph Lyman, DVM	Lexington, KY
David Menard, DVM	Ocala, FL
Ty Wallis, DVM	Knoxville, TN
Beau Whitaker, DVM	Salado, TX
Charles Woodall, DVM	Monument, CO

c. Study Design:

(1) Objective: The objective of this study was to evaluate the clinical effectiveness and field safety of BETAVET for the control of pain and inflammation associated with osteoarthritis in horses.

(2) Study Animals: Horses of any size, sex, or breed, 2 years of age and older, with osteoarthritis in one joint and a lameness score greater than 1/5 on the AAEP Lameness Grading System. A total of 239 horses were enrolled (155 geldings and stallions, 84 mares).

(3) Experimental Design: Within each site on Day 0, an unmasked dispenser randomly assigned each enrolled horse to 1 of 2 treatment groups (BETAVET or saline) in a 1:1 allocation using an electronic data capture (EDC) system. The investigators, owners, and any study personnel involved in making clinical observations were masked to treatment group assignment. The dispenser was unmasked due to the difference in appearance of BETAVET and saline.

(4) Drug Administration: Horses were either administered 1.5 mL BETAVET (2.8 mg/mL betamethasone acetate and 3.2 mg/mL betamethasone sodium phosphate, final market formulation) or 1.5 mL 0.9% sodium chloride (saline) by intra-articular injection into the affected joint once on Day 0.

(5) Measurements and Observations:

(a) Lameness score was the primary variable for effectiveness. Lameness was scored from grade 0-5 on the AAEP Grading System (See Table 2), and was evaluated on Days 0, 1, 3, and 5. A horse was considered a treatment success if the pre-treatment (Day 0) lameness score improved by ≥ 1 grade on Day 5.

(b) Radiographs were performed on Day -5 to Day 0 to confirm osteoarthritis in the affected joint.

(c) Physical examination, and hematology and serum chemistry evaluations were evaluated on Days 0 and 5.

(d) Owners recorded daily observations Days 0-12.

Table 2. AAEP Lameness Grading System

Grade	Description
0	Lameness not perceptible under any circumstance
1	Lameness difficult to observe, not consistently apparent regardless of circumstances (e.g., weight carrying, circling, inclines, hard surfaces)
2	Lameness difficult to observe at a walk or a trot in a straight line, consistently apparent under some circumstances (e.g., weight carrying, circling, inclines, hard surfaces)
3	Lameness consistently observable at a trot under all circumstances
4	Lameness obvious; marked nodding, hitching, and/or shortened stride
5	Lameness obvious, minimal weight-bearing in motion or rest; inability to move

d. Statistical Methods: The primary effectiveness variable was treatment success on Day 5 with superiority established by a statistically significant difference in the proportion of successes in the treated group compared to the saline group and a higher percent success in the treated group. Treatment effect was tested using a generalized linear mixed model analysis with a logit link. The model included the fixed effect of treatment and the random effects site and the treatment-by-site interaction.

e. Results: 229 horses were included in the statistical analysis for effectiveness. Table 3 summarizes the treatment success and failure in each treatment group on Day 5. The treatment success rate for horses in the BETAVET group was statistically significantly different (p=0.0061) than that in the saline group, with respective success rates of 75.73% compared to 52.52% (back-transformed from the logistic regression).

Table 3. Clinical Effectiveness Results

	BETAVET (n=114)	Saline (n=115)
Number of Successes	87	61
Number of Failures	27	54

f. Adverse Reactions: The most common adverse events included local swelling, mild increases in lameness, loose stool, increased heat in the treated joint, depression, anxiety, and inappetance (Table 4). Acute local swelling (within 2 days of injection), depression/lethargy, anxiety, and inappetance occurred more frequently in the BETAVET group. Depression often occurred in combination with another adverse event in the same horse. Several adverse events occurred only in BETAVET treated horses, including dry stool (2 horses), excessive sweating (1 horse), laminitis (1 horse), and acute non-weight bearing lameness (joint sepsis) (1 horse). Some horses experienced more than one adverse event.

One BETAVET treated horse was removed from the study for onset of acute non-weight bearing lameness on Day 4. Treatment for presumed joint sepsis was instituted immediately, but the horse was euthanized several weeks later due to a thromboembolic event associated with prolonged intravenous catheter placement. Serial radiographs following the adverse event revealed further severe joint degeneration when compared to the baseline radiographs. One BETAVET treated horse developed bilateral forelimb lameness on Day 8, with snow packed in the shoes and poor hoof

conformation noted by the investigator. The horse was diagnosed with laminitis. Radiographs showed no abnormalities, and the horse was sound shortly after shoeing changes were implemented.

Table 4. Adverse Reactions

Adverse Reaction	Number (%) of BETAVET Treated Horses	Number (%) of Saline Treated Horses
Acute joint effusion and/or local injection site swelling (within 2 days of injection)	18 (15%)	16 (13%)
Increased lameness (within the first 5 days)	8 (6.7%)	10 (8.3%)
Loose stool	7 (5.9%)	10 (8.3%)
Increased heat in joint	3 (2.5%)	6 (5%)
Depression/lethargy	7 (5.9%)	2 (1.6%)
Agitation/anxiety	5 (4.2%)	3 (2.5%)
Delayed swelling of treated joint (5 or more days after injection)	3 (2.5%)	4 (3.3%)
Inappetance	4 (3.4%)	3 (2.5%)
Dry stool	2 (1.7%)	0 (0%)
Excessive sweating	1 (0.8%)	0 (0%)
Acute non-weight bearing lameness (joint sepsis)	1 (0.8%)	0 (0%)
Laminitis	1 (0.8%)	0 (0%)

g. Conclusion: This field study demonstrates the effectiveness of BETAVET for the control of pain and inflammation associated with osteoarthritis in horses. Treatment with BETAVET may be associated with acute swelling of the treated joint and joint sepsis.

III. TARGET ANIMAL SAFETY:

A. Intra-articular Pharmacokinetic Study

A pharmacokinetic (PK) study in 6 horses was conducted to measure plasma concentrations of betamethasone (BTM), betamethasone acetate (BA) and betamethasone sodium phosphate (BSP) after intra-articular administration of 9 mg of BETAVET. Plasma samples were collected at 0, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 24, 36, 48, 72, 120, 168 hours, and at 10, 14, 21, 28 and 35 days post-administration. There were quantifiable plasma BTM concentrations (above 1.0 ng/mL) from 2-16 hours post-administration, but most of the BSP concentrations and all of the BA concentrations were below the limit of quantification. For BTM, the observed maximum plasma concentration (Cmax) and time to Cmax (Tmax) values ranged from 2.70 to 3.88 ng/mL and 4.5 to 8 hours respectively. The effective terminal elimination half-life (t½) ranged from 3.67 to 7.97 hours. The non-compartmental area-under-the curve to the limit of quantification (AUCLOQ) ranged from 29.24 to 42.96 hr*ng/mL. The study confirmed that BTM was systemically available following intra-articular administration of BETAVET.

B. Margin of Safety Study

1. Title: A 3-Week Evaluation of the Safety of BETAVET IA in Mature Horses. Luitpold Pharmaceuticals: AH-2011-02; SBL: 010-01159. March to April 2012.

2. Study Facility: Southwest Bio-Labs, Inc. (SRL), Las Cruces, NM

3. Study Design:

   a. Objective: To evaluate the safety of BETAVET when administered as an intra-articular injection at 0 (0X), 0.0225 (1X), 0.045 (2X), and 0.09 (4X) mg/lb, for three administrations, five days apart.

   b. Study Animals: Thirty-two healthy horses (16 geldings, 16 non-pregnant, non-lactating mares) of various breeds, 2-18 years of age, weighing between 827 and 1219 pounds.

   c. Experimental Design: The study was conducted using a randomized, masked, controlled, parallel design with 4 animals/sex/treatment.

   d. Treatment Group and Drug Administration:

Table 5. Treatment Groups

Treatment Group	BETAVET Dose	Number (Male/Female)
0x	0 mg/lb*	4/4
1x	0.0225 mg/lb	4/4
2x	0.045 mg/lb	4/4
4x	0.09 mg/lb	4/4

* Control horses were administered saline at a volume equivalent to the volume given to the 4X group.

Horses in all groups received an intra-articular injection into the left front middle carpal joint every five days for a total of three injections. The recommended dose of BETAVET is 9 mg per joint, administered intra-articularly in up to two joints. The 1x dose in this study represents the maximum mg/lb dose that an 800 lb horse would receive (18 mg). The 0x (control group) received an intra-articular injection of saline in the left front middle carpal joint at a volume equivalent to the 4x group. The volumes of injections administered during the study are found in Table 6.

Table 6. Dose Volume Ranges

Group	Day 0 (mL)	Day 5 (mL)	Day 10 (mL)
0x	14.5 to 17	15.5 to 17.5	15.0 to 17.0
1x	3.5 to 5	3.5 to 4.5	3.5 to 4.5
2x	7.0 to 9.5	7.0 to 9.0	7.0 to 9.0
4x	12.5 to 17.5	12.5 to 17.5	12.0 to 17.0

Due to the high volumes being administered to the 0x and 4x groups, synovial fluid was removed prior to dosing. Synovial fluid was not removed from horses in the 1x and 2x groups.

e. Measurements and Observations*:* Daily observations, adverse events, physical examinations, injection site observations, body weights, and clinical pathology. Gross necropsy and histopathology were performed post-mortem.

4. Statistical Analysis: Analysis of variance was used to evaluate all continuous variables. Models included treatment, sex and the treatment-by-sex interaction as fixed effects. For variables measured more than once throughout the study, the following fixed effects were also included: time and the interactions treatment-by-time, sex-by-time and treatment-by-sex-by-time. If pre-treatment values existed, the value closest to the first treatment administration was included as a covariate.

5. Results:

a. Clinical Observations: Injection site reactions were the most common observations in all treatment groups. Injection site reactions were observed within 1 hour of dosing and included swelling at the injection site, lameness/stiffness of the left front limb, and flexing the left front knee at rest (see Table 7).

Table 7. Incidence of Injection Site Reactions Based on Physical Examinations

Group	Total Swelling Observations	Excessive/obvious swelling	Pain at injection site	Knee flexed at rest	Lame or stiff
0x	14	1	0	0	0
1x	6	1	0	0	0
2x	11	2	0	0	0
4x	18	10	3	3	2

The injection site reactions ranged from slight swelling (in many horses on multiple days in all treatment groups) to excessive fluid with swelling, pain, and lameness (4x group). Injection site reactions were observed most commonly on treatment days, and generally decreased in number and severity over subsequent days (see Table 8). The incidence of injection site reactions increased after the second and third injection (number of abnormalities noted on day 10 > day 5 > day 0). In the BETAVET treated groups the number and severity of the injection site reactions were dose dependent. The 4x BETAVET group had the highest overall incidence of and severity of injection site reactions which included heat, swelling, pain, bleeding, and holding the limb up at rest. The control group and 4x group (which received similar injection volumes) had a similar total incidence of injection site reactions; however, the severity of reactions was greater in the 4x group.

Table 8. Number of Horses with Injection Site Reactions* per Day - Noted During Clinical Observations

	Number of Horses with Abnormal Injection Site Observations			
Study Day	Control Group	1x Group	2x Group	4x Group
0**	0	0	0	3
1	3	0	1	3
2	3	0	1	3
3	3	0	1	3
4	3	0	0	3
5**	6	4	4	7
6	2	2	5	4
7	2	1	4	2
8	0	1	3	2
9	0	0	0	0
10**	8	2	7	8
11	1	1	6	8
12	1	1	7	7
13	1	2	6	5
14	0	0	1	1
15	0	0	1	1
16	0	0	0	0

*Findings consisted primarily of swelling, heat, pain, and bleeding.
**Dosing Day

One horse from the 1x group showed lameness from Days 1 to 5 and again on Days 7 to 17 on the left front leg, as noted on the daily clinical observations. The lameness may have been treatment related. However, this animal was noted as moving stiffly to the left on the Study Day -7 physical examination, which may indicate there was a pre-treatment condition.

b. Clinical Pathology: Absolute neutrophils were statistically significantly higher in the BETAVET treated groups as compared to the control group. Trends toward a decrease in lymphocytes and eosinophils, and an increase in monocytes were identified in the BETAVET treated groups after the initial dose of BETAVET. Individual animal values for white blood cells generally remained within the reference range. BETAVET treated horses also had a trend toward increased blood glucose after the initial dose. Some individual animals showed mild increases in blood glucose above the reference range.

Necropsy Findings: At necropsy, macroscopic findings associated with BETAVET were limited to the injection site. Treatment was associated with increased incidence of thickness and synovial discoloration (pink or red) on the synovial side of the injection site. In addition, white foci were observed in the synovial membranes (synovium) of many of the BETAVET treated

injection sites; microthrombus, dark/black foci and black discoloration were observed sporadically. Thickened synovium usually correlated with the microscopic finding of edema; pink, red, or pink or red discoloration correlated with congestion (and occasionally hemorrhage); and microthrombus or dark/black focus or dark discolored correlated with vasculopathy/microthrombus. White foci in the synovium were test article-related and generally correlated with injection site edema.

In the adrenal gland, vacuolation of the cells of the zona fasciculata was observed in 2 males in the 2X group and 2 in the 4X group. This change was minimal in severity and was likely related to treatment.

6. Conclusions: This study supports the safety of BETAVET when administered intra-articularly to horses in a maximum of 2 joints at a one-time dose of 9 mg per joint. Treatment with BETAVET was associated with dose dependent injection site abnormalities (swelling, pain, and lameness).

IV. HUMAN FOOD SAFETY:

This drug is intended for use in horses. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

The product labeling contains the following Warning statement: Do not use in horses intended for human consumption.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to BETAVET:

Not for use in humans. For use in animals only. Keep this and all medications out of the reach of children. Consult a physician in the case of accidental human exposure.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that BETAVET, when used according to the label, is safe and effective for the control of pain and inflammation associated with osteoarthritis in horses.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to diagnose osteoarthritis, properly administer intra-articular injection, provide adequate instructions for post treatment care, and to oversee the treatment of any adverse reactions.

B. Exclusivity:

BETAVET, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug,

and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate safety and effectiveness of BETAVET.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.