Date of Approval: July 30, 2015

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-216

QUEST PLUS Gel

Moxidectin and praziquantel

Oral Gel

Horses

The effect of the supplement is to support safe use in breeding, pregnant, and lactating mares.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-216

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

QUEST PLUS Gel

D. Established Name

Moxidectin and praziquantel

E. Pharmacological Category

Anthelmintic

F. Dosage Form

Oral gel

G. Amount of Active Ingredient

20 mg moxidectin/mL (2.0% w/v) and 125 mg praziquantel/mL (12.5% w/v)

H. How Supplied

QUEST PLUS Gel is available in one syringe applicator size.
Each SURE-DIAL® syringe contains 0.4 oz (11.6 g) of QUEST PLUS Gel which is sufficient to treat a single horse weighing up to 1250 lb, or two or more lighter animals with a combined body weight of up to 1250 lb.

I. Dispensing Status

OTC

J. Dosage Regimen

0.4 mg moxidectin and 2.5 mg praziquantel/kg body weight

K. Route of Administration

Oral

L. Species/Class

Horses

M. Indication

For the treatment and control of the following stages of gastrointestinal parasites in horses and ponies:
Large strongyles:
Strongylus vulgaris – (adults and L_4/L_5 arterial stages)
Strongylus edentatus – (adults and tissue stages)
Triodontophorus brevicauda – (adults)
Triodontophorus serratus – (adults)
Small Strongyles (adults):
Cyathostomum spp., including
Cyathostomum catinatum
Cyathostomum pateratum
Cylicostephanus spp., including
Cylicostephanus calicatus
Cylicostephanus goldi
Cylicostephanus longibursatus
Cylicostephanus minutus
Cylicocyclus spp., including
Cylicocyclus insigne
Cylicocyclus leptostomum
Cylicocyclus nassatus
Cylicocyclus radiatus
Coronocyclus spp., including
Coronocyclus coronatus
Coronocyclus labiatus
Coronocyclus labratus
Gyalocephalus capitatus
Petrovinema poculatus

Small Strongyles:
Undifferentiated lumenal larvae
Encysted cyathostomes:
Late L_3 and L_4 mucosal cyathostome larvae
Ascarids:
Parascaris equorum – (adults and L_4 larval stages)
Pinworms:
Oxyuris equi - (adults and L_4 larval stages)
Hairworms:
Trichostrongylus axei - (adults)
Large-mouth stomach worms:
Habronema muscae - (adults)
Horse stomach bots:
Gasterophilus intestinalis - (2^{nd} and 3^{rd} instars)
Gasterophilus nasalis - (3^{rd} instars)
Tapeworms:
Anoplocephala perfoliata - (adults)

One administration of the recommended dose rate of QUEST PLUS Gel also suppresses strongyle egg production through 84 days.

N. Effect of Supplement

This supplement supports the safe use in breeding, pregnant, or lactating mares.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-216 dated May 14, 2003, contains the dosage characterization information for the approved indication.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-216 dated May 14, 2003 (and supplemental approvals dated March 17, 2004, and November 23, 2005), contains a summary of studies that demonstrate the effectiveness of the drug for the approved indication.

III. TARGET ANIMAL SAFETY

A. Reproductive safety study

1. Title: "Safety Evaluation of Equest Pramox Oral Gel [QUEST PLUS Gel] in Breeding/Pregnant Mares and Their Unborn/Newborn Foals." Study number 1456N-60-10-227.

2. Study Location: Johnson Research, LLC

   Parma, ID

3. Study Design:

   a. Objective: To evaluate the margin of safety of QUEST PLUS Gel in breeding and pregnant mares, and their foals, when administered to mares at three times the recommended dose rate during conception, gestation, and 30 days post-foaling.

   b. Study Animals: 20 pregnant mares between 4 and 17 years old, registered Appaloosa or Quarter Horse breeds

   c. Experimental Design: Following parturition in 2011 ("A" foals), mares were examined for breeding soundness during the first estrus, or foal heat, to determine acceptability for inclusion to the study. On confirmation of normal reproductive status, mares were randomized to one of two treatment groups: Control (tap water) or QUEST PLUS Gel at 3X the recommended dose (1.2 mg/kg moxidectin and 7.5 mg/kg praziquantel). All individuals making clinical observations were masked to treatment group. Mares were bred by live cover on the next estrus, repeating as needed until all mares were pregnant. Mares were maintained in the study through pregnancy, parturition (2012, "B" foals), and 30 days post-foaling. Stallions used in the study were not treated with test article. Two stallions

were used and the mares were paired with the stallion to maintain familial separation and prevent inbreeding of a stallion and mare.

d. Drug Administration: Mares were administered the assigned test article (control or QUEST PLUS Gel) every two weeks starting a few days following the breeding soundness examination, until the mare had received at least 3 doses of test article after the last breeding date. Then, mares were administered the assigned test article once a month through 30 days following the birth of a live foal. All mares received 5-7 doses every two weeks before changing to once monthly dosing.

e. Measurements and Observations:

(1) Breeding Soundness Examinations: Following 2011 parturition, mares were evaluated by rectal palpation and ultrasonography for detection of estrus. Upon detection of foal heat, a breeding soundness exam was performed that consisted of visual evaluation of the vulva, vagina, and cervix; uterine culture; and uterine biopsy.

(2) Ultrasonographic Examinations: Mares were monitored for follicular development and detection of estrus for breeding purposes by ultrasound. Following breeding, mares were checked for pregnancy by ultrasound at least once at each of the following time points: 16-18 days, 28-32 days, 58-62 days, and 88-92 days following the last breeding date.

(3) Physical Examinations: Complete physical examinations of mares were performed on the same day as the breeding soundness exam, 60 days following breeding, around 6 months of gestation, and 30 days following parturition. Complete physical examinations of B foals were performed within 24 hours of birth, and approximately 30 days following birth. During the first physical examination, B foals were assessed for their ability to stand, walk, and suckle, and for congenital abnormalities.

(4) Daily observations: General health observations were conducted on all mares and foals daily during the study.

(5) Clinical observations: Following dosing, mares and their foals were confined to isolation pens for 72 hours. A study veterinarian observed each mare prior to dosing and at approximately 2 hr, 4 hr, and 6 hr following dosing. The veterinarian continued to observe mares twice daily for two more days, and once on the third day prior to returning the mares to pasture.

(6) Clinical Pathology: Blood samples were collected from mares for hematology, serum chemistry, and plasma progesterone prior to initiation of the study, on Day 0 (first treatment day), and approximately every 48 days thereafter. Sample collection occurred 24-48 hours following dosing of test article. Blood samples were collected from B foals for hematology and serum chemistry on Day 2-3 of life, and approximately 30 days post-foaling. Another blood sample was collected from B foals within 24-36 hours of birth for a semi-quantitative detection immunoglobulin G (IgG) concentration.

4. Statistical Methods: Continuous variables were summarized by treatment and time point, including the mean, median, standard deviation, minimum and maximum. Categorical variables were summarized by calculating a frequency distribution of the results by treatment group and time point.

5. Results: Nine of the ten mares in the QUEST PLUS Gel group and eight of the ten control mares gave birth to live foals. One QUEST PLUS Gel-treated mare was removed from the study due to exacerbation of chronic laminitis (pre-existing), and that mare did not get pregnant on two attempts prior to removal from the study. One control mare lost her pregnancy prior to the 28-32 day pregnancy check (early embryonic death) and was removed from the study. One control mare experienced a late-term abortion due to acute focal placentitis. This mare was euthanized shortly after the abortion due to severe chronic laminitis (pre-existing).

   a. Reproductive variables: **Table 1** shows the number of reproductive cycles required for each mare to become pregnant. One QUEST PLUS Gel treated mare had a prolonged time to ovulation following detection of foal heat (at least 39 days from first check). This mare became pregnant on the first breeding and gave birth to a live foal.

Table 1. Number of Estrous Cycles to Conception

Number of Estrous Cycles to Conception	**Control Group: Number of Mares Pregnant/Number of Mares Bred**	**QUEST PLUS Gel Group: Number of Mares Pregnant/Number of Mares Bred**
1	7/10	8/10
2	2/3	1/2
3	1/1	NA*

*One mare with pre-existing laminitis was not pregnant after 2 breedings and was removed from the study before the third breeding due to the severity of the laminitis

Table 2 below compares the mean, median, minimum, and maximum gestation length between the two treatment groups.

Table 2. Gestation Length

	Gestation Length (Days) Control Group	**Gestation Length (Days) QUEST PLUS Gel Group**
Mean	336	332
Median	335	329
Standard Deviation	6.4	7.1
Minimum	325	323
Maximum	346	341

   b. Clinical Pathology: There were no clinically significant abnormalities in blood samples that could be attributed to treatment with the test article.

c. Clinical Observations:

Table 3 lists clinical findings that occurred more frequently in the QUEST PLUS Gel group when compared to control group. Mares in both groups experienced intermittent episodes of diarrhea following dosing. One QUEST PLUS Gel-treated mare experienced episodes that involved depression, inappetence, and diarrhea following 5 out of 17 total doses (29%). This same mare also had one episode of colic. Each episode resolved on its own without medical intervention.

Table 3. Abnormal Clinical Findings in Mares

Abnormal Clinical Findings	Number of Control Mares	Number of QUEST PLUS Gel-treated Mares
Swollen mammary glands around weaning	1	3
Colic	1	3
Retained placenta	0	1
Inappetence	0	1

With the exception of minor trauma and mild diarrhea during mare foal heat, there were no abnormalities noted in A foals prior to weaning and their removal from the study. Of the B foals, 2 control foals and 1 foal from a QUEST PLUS Gel-treated mare were euthanized or died for reasons unlikely related to administration of either control or QUEST PLUS Gel in the mares.

Possible congenital abnormalities were noted in B foals in both the control group and the QUEST PLUS Gel group, and therefore, there was not a clear relationship to treatment. Three abnormalities were recorded for foals from QUEST PLUS Gel-treated mares. One foal had angular limb deformities (carpal valgus) on Day 0 that resolved by Day 30. Another foal had clitoral hypertrophy noted at the Day 30 examination, with some urine dribbling. A third foal had observations shortly after birth of reduced menace and some tongue rolling. The abnormal observations resolved within a few days and the foal was normal at 30 days post-foaling.

6. Conclusions:

This study supports the safe use of QUEST PLUS Gel in breeding, pregnant, and lactating mares. Adverse effects that may be seen following administration of exaggerated doses of QUEST PLUS Gel in mares include inappetence and diarrhea.

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 QUEST PLUS Gel:

"Not for use in humans. Keep this and all drugs out of the reach of children. Do not ingest. If swallowed, induce vomiting. Wash hands and contaminated skin with soap and water. If accidental contact with eyes occurs, flush repeatedly with water. If irritation or any other symptom attributable to exposure to this product persists, consult your physician."

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 QUEST PLUS Gel, when used according to the label, is safe and effective for the treatment and control of gastrointestinal parasites specified on the product label in breeding, pregnant, and lactating mares.

A. Marketing Status

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity

This supplemental approval for QUEST PLUS Gel qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental approval included safety studies. This exclusivity begins as of the date of our approval letter and only applies to reproductive safety in breeding, pregnant, and lactating mares.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(1) or (2)).

D. Patent Information:

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