Questions and answers

EPM

Q: **What is EPM?**
A:

- Equine protozoal myeloencephalitis (EPM) is a neurologic disease of horses
- EPM is caused primarily by the infection with the protozoan parasite *Sarcocystis neurona* (*S. neurona*); a few cases are caused by the protozoan parasite *Neospora hughesi*
- Horses accidentally ingest the protozoan parasites when consuming feed and/or water contaminated by infected opossum feces

Q: Is EPM a common neurologic disease in horses?
A:

- It is estimated that approximately 50 percent of horses in many regions of the U.S. have been exposed to *S. neurona*
- Horses in some regions of the U.S. may have an exposure rate closer to 70 percent to 80 percent
- However, less than 1 percent of horses actually develop clinical signs of EPM

Q: Can EPM be prevented?
A:

- Currently, there is no vaccine on the market that aids in prevention of EPM
- The best way to minimize the risk of EPM is through management practices such as:
    - Protecting feed and water sources from opossums to avoid contamination with *S. neurona* sporocysts
    - Reducing exposure to areas inhabited by opossums
    - Reducing the horse's stress levels as much as possible to avoid suppressing the immune system

Q: Are some horses more susceptible to EPM than others?
A:

- EPM is not specific to a certain age, breed, gender or discipline, although some studies demonstrated an increased incidence among race horses and western performance horses. Cases of EPM in horses less than 1 year of age are rare
- Any horse living in an area with an opossum population is susceptible. Opossums are found only in North and South America. In the U.S., opossums generally reside everywhere except the mountain west and western desert areas
- Some of the potential risk factors for EPM may include:
    - Living in proximity to a wooded area
    - Living on the same farm as a currently and/or previously EPM-infected horse
    - Exposure to a stressful event such as travel, relocation, heavy training, or recent illness or injury

Q: Why is EPM difficult to diagnose?
A:

- EPM is a master of disguise and can look like many other neurologic diseases or obscure lameness
- Clinical signs vary by horse and can include:
  - Ataxia, incoordination
  - Asymmetric muscle atrophy
  - Weakness
  - Head tilt
  - Difficulty swallowing
  - Ear droop
  - Lameness
  - Behavior change
  - Unexplainable decrease in performance
- There are several tests currently used for diagnosing EPM – Western blot, IFAT and SAG-ELISA are the most common
- While testing is highly recommended, no single test is 100 percent accurate
- Tests performed on blood indicate if a horse has been exposed to *S. neurona,* but do not necessarily confirm active infection. A positive test result using a spinal fluid sample, free of blood, is more suggestive of active infection
- A thorough neurologic exam accompanied by testing is the most effective way to diagnose EPM

Q: What is the Mayhew neurologic scale and how is it used to diagnose EPM?
A:

- When diagnosing EPM, the Mayhew neurologic scale is used to determine the severity of clinical signs during neurologic exams
- The scale ranges from 0 to 5
  - 0 = Normal
  - 1 = Deficits detectable at normal gaits
  - 2 = Deficits obvious at normal gaits
  - 3 = Deficits prominent at normal gaits; horse may buckle or fall when manipulated (such as during tail pull and limb placement tests)
  - 4 = Profound deficits at normal gaits; frequently stumbles; horse may fall when manipulated
  - 5 = Recumbent (unable to rise)

Q: Once a horse contracts EPM, can it become infected again?
A:

- It is possible for horses to relapse after they recover from EPM
- It is estimated that at least 10 percent of horses that recover from EPM will relapse within 60 to 90 days following treatment
- Clinical signs detected during a relapse typically mimic the same neurologic signs the horse demonstrated when EPM was diagnosed initially

Q: What are the chances of a horse recovering from EPM?
A:

- Less than 30 percent of horses that contract EPM will fully recover, although 60 percent to 70 percent show clinical improvement with early treatment
- Early diagnosis and treatment help minimize the damage caused by *S. neurona*

Protazil®

Q: What is Protazil?
A:

- Protazil is a diclazuril-based anti-protozoal top-dress pellet for the treatment of EPM caused by *S. neurona* in horses

Q: What is diclazuril?
A:

- Diclazuril is an FDA-approved anti-protozoal drug used for the treatment of EPM in horses
- Diclazuril has proved safe and effective in treating horses naturally infected with EPM

Q: What are the benefits of treating EPM with Protazil?
A:

- Protazil is the only EPM treatment available in an alfalfa-based, pelleted, top-dress, formula
- Protazil is easier to administer than a paste EPM treatment product
- Protazil is voluntarily consumed by most horses when administered on their daily grain ration
- Protazil offers convenient dosing with an easy-to-use calibrated scoop
- Protazil is the only FDA-approved diclazuril-based EPM treatment product on the market

Q: How does Protazil differ from other EPM treatment products on the market?
A:

- Protazil is the only EPM treatment product in an alfalfa-based, pelleted, top-dress formula, making accurate dosing and administration easier
- Protazil is a more affordable FDA-approved EPM treatment option
- The alfalfa-based pellet formulation helps ensure voluntary consumption by the horse

Q: Is Protazil safe?
A:

- In a large field safety study of 214 privately owned EPM-positive horses of various genders, breeds and ages, Protazil was administered for 28 days at doses of 1, 5 and 10 milligrams of diclazuril per kilogram of body weight (mg/kg)
- Adverse events were reported for two of the 214 horses. In the first case, a horse was enrolled showing severe neurologic signs. Within 24 hours of dosing, the horse was recumbent, biting, and exhibiting signs of dementia. The horse died, and no cause of death was determined. In the second case, the horse began walking stiffly approximately 13 days after the start of dosing. The referring veterinarian reported that the horse had been fed grass clippings and possibly had laminitis

Q: Is Protazil easy to use?
A:

- Protazil is simply poured on top of the horse's daily grain ration, increasing client compliance and voluntary consumption by the horse and avoiding the tubes and mess of other treatment products
- Each container of Protazil comes with an easy-to-use calibrated scoop that can be adjusted for the weight of each individual horse

Q: Can Protazil be used for preventive treatment?

A:

- Currently, Protazil is not labeled for preventive treatment

Q: Can Protazil be fed to stallions or broodmares?

A:

- The safe use of Protazil in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated

Q: Where is Protazil sold?

A:

- Protazil is sold exclusively to licensed veterinarians and is available in 2- and 10-pound containers

Q: Does Protazil have any contraindications, precautions or warnings associated with its use?

A:

- Contraindications
  - Use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril.
- Warnings
  - For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.
- Precautions
  - The safe use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. The safety of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets with concomitant therapies in horses has not been evaluated.

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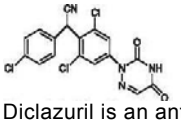
FOR ORAL USE IN HORSES ONLY

For the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

CAUTION
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
NADA #141-268 Approved by FDA

DESCRIPTION
Diclazuril, (±)-2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl) benzeneacetonitrile, has a molecular formula of $C_{17}H_9Cl_3N_4O_2$, a molecular weight of 407.64, and a molecular structure as follows:



Diclazuril is an anticoccidial (antiprotozoal) compound with activity against several genera of the phylum Apicomplexa. PROTAZIL® (diclazuril) is supplied as oral pellets containing 1.56% diclazuril to be mixed as a top-dress in feed. Inert ingredients include dehydrated alfalfa meal, wheat middlings, cane molasses and propionic acid (preservative).

INDICATIONS
PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets are indicated for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

DOSAGE AND ADMINISTRATION
Dosage: PROTAZIL® (1.56% diclazuril) is administered as a top dress in the horse's daily grain ration at a rate of 1 mg diclazuril per kg (0.45 mg diclazuril/lb) of body weight for 28 days. The quantity of PROTAZIL® necessary to deliver this dose is 64 mg pellets per kg (29 mg pellets/lb) of body weight.

Administration: To achieve this dose, weigh the horse (or use a weigh tape)). Scoop up PROTAZIL® to the level (cup mark) corresponding to the dose for the horse's body weight using the following chart:

Weight Range of Horse (lb)	mLs of Pellets	Weight Range of Horse (lb)	mLs of Pellets
275 - 524	20	1275 - 1524	60
525 - 774	30	1525 - 1774	70
775 - 1024	40	1775 - 2074	80
1025 - 1274	50	-	-

One 2-lb bucket of PROTAZIL® will treat one 1100-lb horse for 28 days. One 10-lb bucket of PROTAZIL® will treat five 1100-lb horses for 28 days.

CONTRAINDICATIONS
Use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril.

WARNINGS
For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.

PRECAUTIONS
The safe use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. The safety of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets with concomitant therapies in horses has not been evaluated.

ADVERSE REACTIONS
There were no adverse effects noted in the field study which could be ascribed to diclazuril. To report suspected adverse reactions, to obtain a MSDS, or for technical assistance call **1-800-224-5318**.

CLINICAL PHARMACOLOGY
The effectiveness of diclazuril in inhibiting merozoite production of *Sarcocystis neurona* and *S. falcatula* in bovine turbinate cell cultures was studied by Lindsay and Dubey (2000).[1] Diclazuril inhibited merozoite production by more than 80% in cultures of *S. neurona* or *S. falcatula* treated with 0.1 ng/mL diclazuril and greater than 95% inhibition of merozoite production (IC_{95}) was observed when infected cultures were treated with 1.0 ng/mL diclazuril. The clinical relevance of the in vitro cell culture data has not been determined.

PHARMACOKINETICS IN THE HORSE

The oral bioavailability of diclazuril from the PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at a 5 mg/kg dose rate is approximately 5%. Related diclazuril concentrations in the cerebrospinal fluid (CSF) range between 1% and 5% of the concentrations observed in the plasma. Nevertheless, based upon equine pilot study data, CSF concentrations are expected to substantially exceed the in vitro IC_{95} estimates for merozoite production (Dirikolu et al., 1999)[2]. Due to its long terminal elimination half-life in horses (approximately 43-65 hours), diclazuril accumulation occurs with once-daily dosing. Corresponding steady state blood levels are achieved by approximately Day 10 of administration.

EFFECTIVENESS

Two hundred and fourteen mares, stallions, and geldings of various breeds, ranging in age from 9.6 months to 30 years, were enrolled in a multi-center field study. All horses were confirmed EPM-positive based on the results of clinical examinations and laboratory testing, including CSF Western Blot analyses. Horses were administered PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at doses of 1, 5, or 10 mg diclazuril/kg body weight as a top-dress on their daily grain ration for 28 days. The horses were then evaluated for clinical changes via a modified Mayhew neurological scale on Day 48 as follows:

0. Normal, neurological deficits not detected.
1. Neurological deficits may be detectable at normal gaits; signs exacerbated with manipulative procedures (e.g., backing, turning in tight circles, walking with head elevation, truncal swaying, etc.).
2. Neurological deficit obvious at normal gaits or posture; signs exacerbated with manipulative procedures.
3. Neurological deficit very prominent at normal gaits: horses give the impression they may fall (but do not) and buckle or fall with manipulative procedures.
4. Neurological deficit is profound at normal gait: horse frequently stumbles or trips and may fall at normal gaits or when manipulative procedures were utilized.
5. Horse is recumbent, unable to rise.

Each horse's response to treatment was compared to its pre-treatment values. Successful response to treatment was defined as clinical improvement of at least one grade by Day 48 ± conversion of CSF to Western Blot-negative status for *S. neurona* or achievement of Western Blot-negative CSF status without improvement of 1 ataxia grade.

Forty-two horses were initially evaluated for effectiveness and 214 horses were evaluated for safety. Clinical condition was evaluated by the clinical investigator's subjective scoring and then corroborated by evaluation of the neurological examination videotapes by a masked panel of three equine veterinarians. Although 42 horses were evaluated for clinical effectiveness, corroboration of clinical effectiveness via videotape evaluation was not possible for one horse due to missing neurologic examination videotapes. Therefore, this horse was not included in the success rate calculation.

Based on the numbers of horses that seroconverted to negative Western Blot status, and the numbers of horses classified as successes by the clinical investigators, 28 of 42 horses (67%) at 1 mg/kg were considered successes. With regard to independent expert masked videotape assessments, 10 of 24 horses (42%) at 1 mg/kg were considered successes. There was no clinical difference in effectiveness among the 1, 5, and 10 mg/kg treatment group results.

Adverse events were reported for two of the 214 horses evaluated for safety. In the first case, a horse was enrolled showing severe neurologic signs. Within 24 hours of dosing, the horse was recumbent, biting, and exhibiting signs of dementia. The horse died, and no cause of death was determined. In the second case, the horse began walking stiffly approximately 13 days after the start of dosing. The referring veterinarian reported that the horse had been fed grass clippings and possibly had laminitis.

ANIMAL SAFETY

PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 30 horses (15 males and 15 females, ranging from 5 to 9 months of age) in a target animal safety study. Five groups of 6 horses each (3 males and 3 females) received 0, 5 (5X), 15 (15X), 25 (25X) or 50 (50X) mg diclazuril/kg (2.27mg/lb) body weight/day for 42 consecutive days as a top-dress on the grain ration of the horse. The variables measured during the study included: clinical and physical observations, body weights, food and water consumption, hematology, serum chemistry, urinalysis, fecal analysis, necropsy, organ weights, gross and histopathologic examinations. The safety of diclazuril top-dress administered to horses at 1 mg/kg once daily cannot be determined based solely on this study because of the lack of an adequate control group (control horses tested positive for the test drug in plasma and CSF). However, possible findings associated with the drug were limited to elevations in BUN, creatinine, and SDH and less than anticipated weight gain. Definitive test article-related effects were decreased grain/top-dress consumption in horses in the 50 mg/kg group.

In a second target animal safety study, PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 24 horses (12 males and 12 females, ranging from 2 to 8 years of age). Three groups of 4 horses/sex/group received 0, 1, or 5 mg diclazuril/kg body weight/day for 42 days as a top-dress on the grain ration of the horse. The variables measured during the study included

physical examinations, body weights, food and water consumption, hematology, and serum chemistry. There were no test article-related findings seen during the study.

STORAGE INFORMATION
Store between 15°C to 30°C (59°F to 86°F).

HOW SUPPLIED
PROTAZIL® (1.56 % diclazuril) Antiprotozoal Pellets are supplied in 2-lb (0.9 kg) and 10-lb (4.5 kg) buckets.

REFERENCES
1. Lindsay, D. S., and Dubey, J. P. 2000. Determination of the activity of diclazuril against *Sarcocystis neurona* and *Sarcocystis falcatula* in cell cultures. *J. Parasitology*, 86(1):164–166.

2. Dirikolu, L., Lehner, F., Nattrass, C., Bentz, B. G., Woods, W. E., Carter, W. E., Karpiesiuk, W. G., Jacobs, J., Boyles, J., Harkins, J. D., Granstrom, D. E. and Tobin, T. 1999. Diclazuril in the horse: Its identification and detection and preliminary pharmacokinetics. *J. Vet. Pharmacol. Therap.* 22:374–379.

May 2010
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