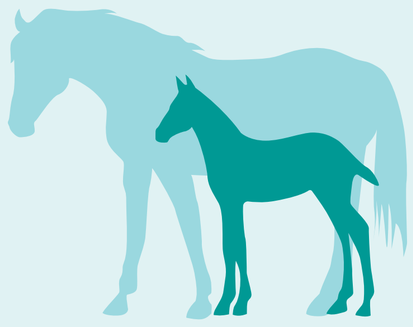
EQUINE PROTOZOAL MYELOENCEPHALITIS (EPM)

QUICK FACTS

What is EPM?

EPM is an infectious, progressive neurological disease that affects horses following environmental exposure to opossum feces. EPM can cause devastating and lasting neurological damage and any horse is susceptible.

- Caused by infection with the parasite Sarcocystis neurona (S. neurona); less frequently with Neospora hughesi (N. hughesi)[1]
- Up to 90% of the U.S. horse population has been exposed to S. neurona, depending on geographic location[1]
- Not all horses infected with S. neurona or N. hughesi will develop disease



EPM Risk Factors[1]

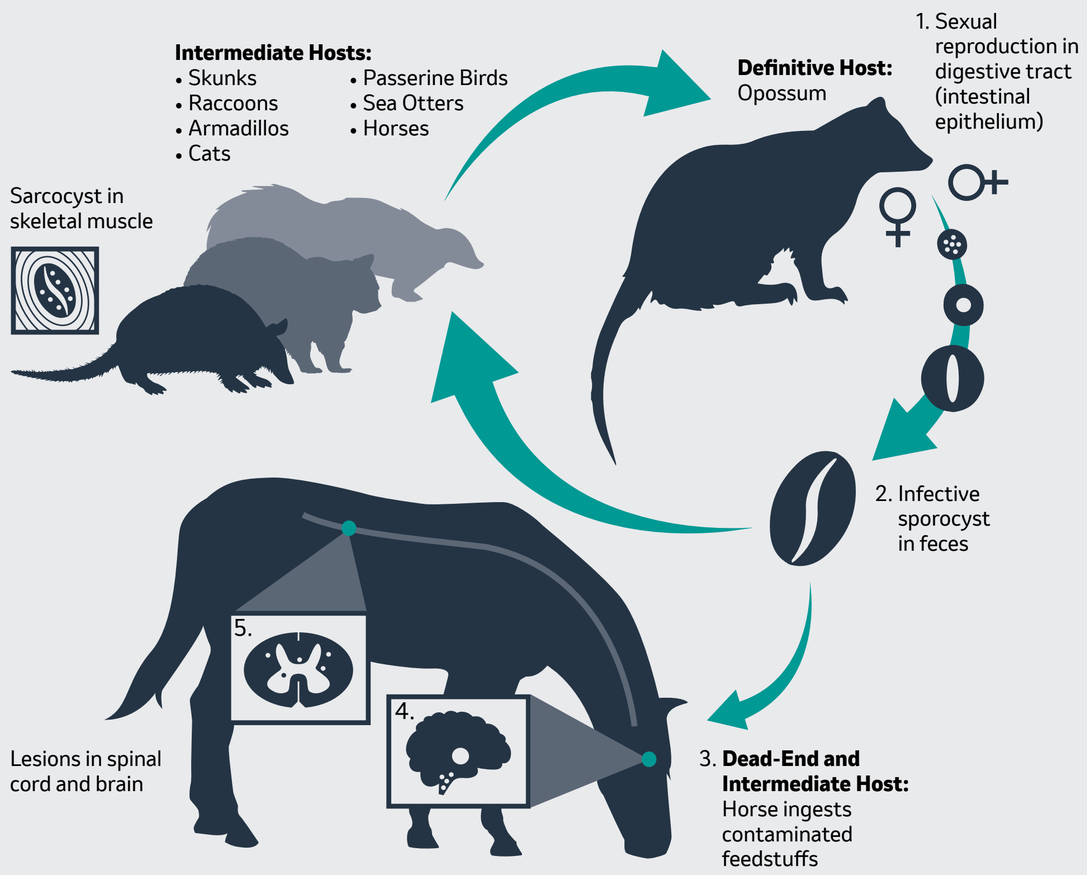
- Exposure to wildlife; presence of opossums
- Stress associated with illness, transport, strenuous exercise
- Young horses (1–5 years)
- Horses used for western performance, racing and other strenuous activities
- Immune-compromised horses of any age
- Immunosuppression associated with concurrent conditions
- Commonly seen in late summer and fall, but can occur any time

Lifecycle of Sarcocystis neurona[1]

1. The S. neurona organism is ingested by the definitive host, the opossum, by scavenging on intermediate hosts (cats, raccoons, skunks, armadillos, sea otters) that carry sarcocyst in skeletal muscle
2. The infective stage of the organism (the sporocysts) is passed in the opossum's feces
3. The horse (dead-end host*) acquires the infective sporocysts while grazing or eating contaminated feed or drinking water
4. Once ingested by the horse, the sporocysts migrate from the intestinal tract into the bloodstream and cross the blood/brain barrier
5. The resulting inflammatory response to sporocyst presence injures the horse's central nervous system

(The definitive or intermediate hosts for N. hughesi have not yet been identified.)[1]

*Evidence exists supporting horses as intermediate as well as dead-end hosts.[2]



Evidence cysts can live in skeletal musculature of horse (without perpetuating life cycle).[2]

Watch for These Signs

- Gait abnormalities
- Ataxia (incoordination)
- Stumbling
- Muscle atrophy
- Weakness
- Lethargy
- Inability to chew or swallow
- Head tilt, ear droop
- Behavior change
- Blindness
- Seizures

Contact your veterinarian immediately if your horse exhibits neurological signs. Horses that are diagnosed early and treated aggressively have the best chance for recovery.

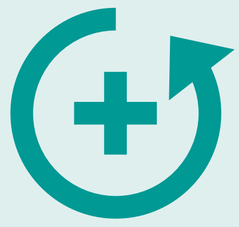
Diagnosis

Diagnosing EPM is difficult because it can mimic other neurologic diseases.

- Complete neurologic and physical exam to rule out other diseases
- Blood and cerebrospinal fluid (CSF) analysis to detect antiprotozoal antibodies

Treatment and Recovery

- An FDA-approved EPM treatment such as PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets will be prescribed to control infection
- Additional supportive treatment may be recommended based on the severity of neurologic deficits and associated complications
- 60–70% of horses show clinical improvement with early treatment[1]



IMPORTANT SAFETY INFORMATION

Use of PROTAZIL® is contraindicated in horses with known hypersensitivity to diclazuril. The safety of Protazil in horses used for breeding purposes, during pregnancy, or in lactating mares, and use with concomitant therapies in horses has not been evaluated. Do not use in horses intended for human consumption. Not for human use. For complete safety information, refer to the product label.

[1]Reed SM, et al. Equine Protozoal Myeloencephalitis: An Updated Consensus Statement with a Focus on Parasite Biology, Diagnosis, Treatment and Prevention. J Vet Intern Med 2016;30:491–502.
[2]T. Mullaney, et al. Evidence to support horses as natural intermediate hosts for Sarcocystis neurona. Veterinary Parasitology; 133 (2005) 27-36.

Brought to you by:

PROTAZIL®
(1.56% diclazuril) Antiprotozoal Pellets

The Science of Healthier Animals

MERCK Animal Health

NAC NO.: 1047378.2

PROTAZIL®

Intervet/Merck Animal Health

ANTIPROTOZOAL PELLETS

(1.56% DICLAZURIL)

FOR ORAL USE IN HORSES ONLY

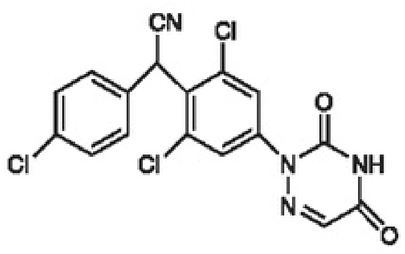
CAUTION

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Approved by FDA under NADA #141-268,

DESCRIPTION

Diclazuril, (±)-2,6-dichloro-a-(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 Horses (lb)	mLs of Pellets
275–524	**20**
525–774	**30**
775–1024	**40**
1025–1274	**50**
1275–1524	**60**
1525–1774	**70**
1775–2074	**80**

One 2.4-lb bucket of PROTAZIL® will treat one 1274-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 3 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 topdress 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 2.4-lb (1.1 kg) and 10-lb (4.5 kg) buckets.

REFERENCE

1. Lindsay, D. S., and Dubey, 1. 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.

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2.4 lbs (1.1 kg)	**Rev. 11/2022 167863 R2**

CPN: 1047490.4

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(1.56% diclazuril)
Antiprotozoal Pellets