EPM Recovery Starts with Protazil®
(1.56% diclazuril)

Safe, easy and effective, Protazil® starts working fast against disease where time matters.

- The first and only FDA-approved alfalfa-based, pelleted formulation containing diclazuril
- Rapid absorption and no loading dose required[1]
- Makes accurate dosing and administration easier and safer for owners
- Well accepted by horses and consumed with no mess or fuss
- Proven safe in animal safety trials[2]
- Proven efficacy in multi-state clinical field trial[2]
- Administer as a daily top-dress at 1 mg/kg for 28 days
- Available in 2.4 pound container

FDA APPROVED

Protazil Pharmacokinetics

- Labeled dose of 1 mg/kg attained plasma and CSF drug concentrations known to inhibit *Sarcocystis neurona*
- Active ingredient, diclazuril, quickly reaches therapeutic levels
- Plasma drug concentrations well above minimum inhibitory concentration (MIC=1ng/mL) within 12 hours of administering a single dose
- Long elimination half-life

Diclazuril Pharmacokinetics 1 mg/kg at Steady State[1]

T_{max} (Time to reach peak plasma concentration)	226 hours ~9.4 days
C_{max} (Maximum plasma concentration)	910 ng/ml
t ½ (Elimination half-life)	54.3 hours ~2.3 days
CSF concentration at steady state	26 ng/ml

RAPID ABSORPTION OF DICLAZURIL WITHOUT A LOADING DOSE

"EPM is a serious disease threat in Ohio. The Protazil treatment regimen achieves therapeutic blood levels quickly and without a loading dose. I've used Protazil to treat my own horses and client horses too. Protazil is easy to use, horses find the pellets palatable plus it's priced competitively. Protazil has an excellent safety profile, is FDA-approved and backed by Merck Animal Health. Horse owners appreciate that assurance."

Daniel Yates, D.V.M. — Wilmington, Ohio

"We have been using Protazil in our practice with excellent results. Client compliance in treatment has increased due to the ease of administration and palatability of Protazil over oral pastes. We've observed some horses will preferentially eat the Protazil over concentrate feeds. With increased client compliance we can achieve better treatment results with our patients and better outcomes for our clients."

Greggory S. Bell, D.V.M. — Pagosa Springs, Colorado

IMPORTANT SAFETY INFORMATION

Use of Protazil® (1.56% diclazuril) is contraindicated in horses with known hypersensitivity to diclazuril.
Safe use in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated.
The safety of Protazil® (1.56% diclazuril) with concomitant therapies in horses has not been evaluated.
For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children. For complete information, refer to the product label.

[1] Hunyadi L, Papich MG, Pusterla N. Pharmacokinetics of a low-dose and FDA-labeled dose of diclazuril administered orally as a pelleted top dressing in adult horses. J of Vet Pharmacology and Therapeutics (accepted) 2014, doi: 10.111/jvp.12176. The correlation between pharmacokinetic data and clinical effectiveness is unknown

[2] HR Freedom of Information Summary Data on file at Merck Animal Health

PROTAZIL®

ANTIPROTOZOAL PELLETS *(1.56% diclazuril)*

FOR ORAL USE IN HORSES ONLY

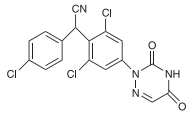
For the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

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 2.4-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 ± 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 2.4 lb (1.1 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.

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2.4 lbs (1.1 kg)	07-2014
10 lbs (4.5 kg)	09-2011

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