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YOUR GUIDE TO EQUINE HEALTH CARE

FACT SHEET

Equine Protozoal Myeloencephalitis

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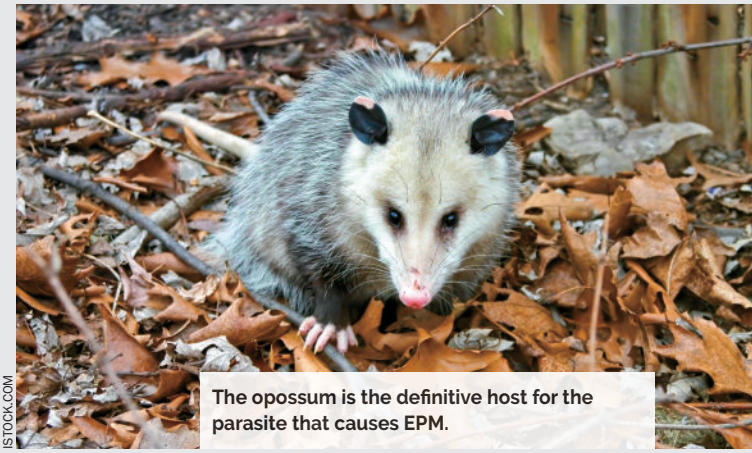
A well-known cause of neurologic disease in horses, EPM is considered a diagnosis of exclusion



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The opossum is the definitive host for the parasite that causes EPM.

Equine protozoal myeloencephalitis (EPM) was first recognized in the mid- to late-1960s as a "segmental myelitis." It wasn't until 1974 that scientists identified a single-celled parasite that prompted the name change to equine protozoal myeloencephalitis.[1] We now know two parasites, *Sarcocystis neurona* or *Neospora hughesi*, can cause EPM, but most cases are caused by *S. neurona*.

How *S. Neurona* Causes Disease

Opossums are the definitive hosts for *S. neurona*. They become infected by scavenging on intermediate hosts (skunks, cats, raccoons, armadillos) with *S. neurona* sarcocysts—walled-off "pockets" containing the infectious form of the parasite, which has reproduced here asexually—in their muscles. Once ingested, mature sarcocysts release bradyzoites, which transform and reproduce sexually in the small intestine, producing oocytes. The opossum sheds fully sporulated oocysts or sporocysts in its feces. They contaminate the environment and infect intermediate hosts when consumed.

Horses are incidental hosts that become infected by consuming the sporocysts in the environment. Unlike intermediate hosts, horses—as incidental or aberrant intermediate hosts—do not serve as reservoirs for infecting opossums (i.e., sarcocysts do not form that opossums later consume) and do not spread *S. neurona* directly to other horses.

Once ingested, what happens to those sporocysts remains unclear. Researchers know they release sporozoites, which travel to the spinal cord but not how and when. They also don't know why the sporozoites migrate to the spinal cord in some horses but not others.[1,2]

Picking and Choosing its Victims

Exposure to *S. neurona* is common, but infection is rare. For example, anywhere from 15-89% of horses have antibodies to *S. neurona* in their bloodstream, indicating they've been exposed to the parasite; however, the annual incidence of disease is less than 1%. In other words, infection does not equate to disease.[1-3]

Risk Factors

Horses diagnosed with EPM are often younger than 4 or older than 13. The highest number of cases occur in the fall and the fewest in winter. When caretakers prevent wildlife access to horse feed, the likelihood of disease drops by one-third.

Stress might increase a horse's chances of developing EPM. Specifically, immune compromise, heavy exercise, transport, injury, surgery, or foaling increase a horse's chances of infection resulting in clinical disease.[1,3]

The Shadowy Face of EPM

When the parasite spreads throughout the horse's body, it can "land" anywhere in the brain, brainstem, or spinal cord. Thus, every case is unique (i.e., EPM has no "classic" presentation).

Horses typically exhibit signs consistent with spinal cord injury, such as ataxia (incoordination), gait abnormalities that can mimic lameness, and muscle weakness and/or atrophy.[1-3] Less commonly, horses have encephalopathic (brain) manifestations such as cranial nerve deficits manifesting as dysphagia (difficulty swallowing, abnormal airway function) or abnormal behavior and state of consciousness or even seizures.[1-3]

The parasite can infect both white and gray matter anywhere in the brain or along the spinal cord.[1,3] The parasites can be found in multiple locations with no apparent pattern.

One relatively consistent finding, however, is asymmetric neurologic deficits and focal muscle atrophy in affected horses. This is because the parasites do not affect both sides of the brain or spinal cord evenly. Further, the disease can begin acutely or have an insidious onset. In either case it is progressively debilitating.[1-3]

A Diagnostic Challenge: Exclusion Is Key

Albeit an uncommon disease, EPM is still the most common infectious neurologic disease diagnosed in horses. Vets must always consider EPM in horses displaying signs consistent with central nervous system (CNS) disease and distinguish EPM from lameness, which is not always easy.[2,4,5]

The long list of neurologic conditions vets must distinguish EPM from includes cervical vertebral stenotic myelopathy, equine herpesvirus-1 myeloencephalopathy (EHM), rabies, toxins, trauma, Lyme neuroborreliosis, equine degenerative myelopathy, and more.[1] Recently, scientists identified *Toxoplasma gondii* as another parasite capable of causing EPM-like disease in horses.[6]

Currently, the only way to definitively diagnose EPM is to identify parasites in the brain or spinal cord post-mortem. Even then, parasites are identified in fewer than 50% of cases with other characteristic microscopic changes (e.g., inflammatory changes in the brain and spinal cord). This approach is not helpful in a clinical setting, and laboratory testing must be performed in conjunction with a comprehensive clinical examination.[1,2]

Simply detecting antibodies against *S. neurona* or *N. hughesi* in the horse's bloodstream has minimal diagnostic value. Only if a horse is negative can you rule out EPM (although there are exceptions to this rule in very acute cases). Even the presence of antibodies in the cerebrospinal fluid (CSF) bathing the brain and spinal cord does not definitively diagnose EPM, because antibodies can passively diffuse from the bloodstream into the CSF.

Therefore, the serum:CSF antibody titer ratio is

veterinarians' test of choice. This reveals whether antibody levels are higher in CSF than expected from simple diffusion of the antibodies from the bloodstream across the blood-brain-barrier into the CSF. It supports intrathecal (i.e., within the CSF) production of antibodies against the parasite within the CNS.

Important point: Do not measure antibody levels as part of a prepurchase exam to determine if a horse is EPM-free. And do not use antibody tests when trying to distinguish lameness from neurologic disease, which can be a challenging task.[2]

Treatment

Veterinarians have a variety of FDA-approved drugs they can prescribe for horses with EPM:

Triazines Both diclazuril and ponazuril are coccidiostats FDA-approved for use in horses. Evidence suggests these medications target *S. neurona*'s "apicoplast organelle," which mammalian cells do not contain.[2,7]

Treatment tip: Administer with corn oil to increase serum/CSF concentrations of these drugs.

Folate-inhibiting drugs An FDA-approved combination of sulfadiazine and pyrimethamine blocks folate synthesis in *S. neurona*, which is necessary for the parasite's survival.[2,7]

Treatment tip: Do not feed hay for two hours before or after administering oral pyrimethamine.

Vitamin E This potent antioxidant is often given to horses with EPM because researchers believe the damaged CNS is susceptible to oxidant injury.[1]

Prognosis

Clinical improvement rates using any of the FDA-approved treatments range from 57% to 62%. Approximately 10% of horses relapse within one to three years of discontinuing treatment.[7]

Prevention

The most common recommendation for preventing EPM is ensuring opossums do not have access to your horse's feed and water. In addition, decreasing stress and optimizing overall health can improve horses' immune defenses, potentially protecting them from parasitic infection. Intermittent treatment with low doses of triazines might help reduce infections.[8]

Summary

EPM, despite being rare, is an important neurologic disease of horses. To make an accurate diagnosis, veterinarians must perform the following:[1-3]

1. Confirm clinical signs are consistent with spinal cord/brain dysfunction.
2. Exclude all other causes of neurologic disease.
3. Use paired serum:CSF samples to confirm antibody production against the parasite in the CSF.

We don't know why EPM infects some horses but not others, making additional research essential for developing improved preventive and therapeutic strategies.

Recommended Resources

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Boehringer Ingelheim

Approved by FDA under NADA # 141-188

Marquis®

(15% w/w ponazuril)
Antiprotozoal Oral Paste

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

For the Treatment of Equine Protozoal Myeloencephalitis (EPM) in Horses

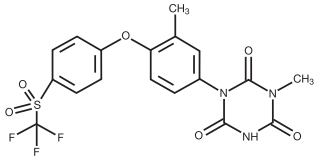
For Oral Use Only

Description: MARQUIS® (15% w/w ponazuril) Antiprotozoal Oral Paste is supplied in a ready-to-use syringe containing 127 grams of paste. Each gram of paste contains 150 mg of ponazuril (15% w/w). MARQUIS is designed to be delivered as an orally administered paste.

Each syringe barrel of MARQUIS contains enough paste to treat one (1) 1,200 lb (544 kg) horse for seven (7) days, at a dose rate of 5 mg/kg (2.27 mg/lb) body weight or to treat one 1,200 lb (544 kg) horse with a single loading dose of 15 mg/kg (6.81 mg/lb) body weight and for four days subsequently at a rate of 5 mg/kg (2.27 mg/lb) body weight. The plunger contains a dosage ring calibrated for a dose rate of 5 mg/kg (2.27 mg/lb) body weight and marked for horse weight from 600 to 1,200 lbs (272 to 544 kg). The syringe barrel is packaged with a plunger. The syringe barrels are packaged in units of four with four plungers and in single syringe units with one plunger.

Ponazuril is an anticoccidial (antiprotozoal) compound with activity against several genera of the phylum Apicomplexa.

Chemical nomenclature and structure: Ponazuril 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione,1-methyl-3-[3-methyl-4-[4-[(trifluoromethyl)sulfonyl] phenoxy]phenyl]-(9CI)



Clinical pharmacology: The activity of ponazuril has been demonstrated in several Apicomplexans[1-6]. Lindsay, Dubey and Kennedy[7] showed that the concentration of ponazuril necessary to kill Sarcocystis neurona in vitro was 0.1 to 1.0 µg/mL. Furr and Kennedy[8] evaluated the pharmacokinetics of ponazuril in serum and CSF in normal horses treated daily at 5 mg/kg for 28 days. The time to peak serum concentration (T_{max}) was 18.20 (±5.9) days and the maximum serum concentration (C_{max}) was 5.59 (±0.92) µg/mL. The terminal elimination half-life for serum (calculated using Day 28 to 42 data) was 4.50 (±0.57) days. In CSF, T_{max} was 15.40 (±7.9) days and C_{max} was 0.21 (±0.072) µg/mL.

A pharmacokinetic study was conducted in eight horses to collect serum and cerebrospinal fluid (CSF) levels of ponazuril after a single dose of 5 mg/kg body weight. The estimated parameter values were used to model time concentration profiles for ponazuril in serum and CSF. The model results were used to estimate the size of the loading dose needed to support the achievement of steady state serum and CSF levels after the first dose. The appropriate loading dose, calculated on the basis of the accumulation ratio (i.e., the fold increase in serum drug concentrations once steady state conditions have been achieved) was 15 mg/kg (6.81 mg/lb) body weight. This dose represents the range of estimated accumulation ratios of 2.3 to 3.3. Thus, a three-fold loading dose (3*5 mg/kg) was selected, leading to achievement of steady state blood levels in horses after one or two days of ponazuril administration.

Indications: MARQUIS is indicated for the treatment of equine protozoal myeloencephalitis (EPM) caused by Sarcocystis neurona.

Effectiveness Summary: A field study was conducted at six sites with seven investigators across the United States.[9] The study was conducted using historical controls. In this study, each animal's response to treatment was compared to its pre-treatment values. The following standardized neurologic scale was used to grade the horses:

0 Normal, no deficit detected

1 Deficit just detected at normal gait

2 Deficit easily detected and is exaggerated by backing, turning, swaying, loin pressure or neck extension

3 Deficit very prominent on walking, turning, loin pressure or neck extension

4 Stumbling, tripping and falling down spontaneously

5 Recumbent, unable to rise

Improvement was defined as a decrease of at least one grade.

Naturally-occurring clinical cases of EPM, characterized by signalment and laboratory diagnosis, were randomly allotted to one of two treatment doses (5 or 10 mg/kg/day for a period of 28 days), then evaluated for clinical changes through 118 days.

Acceptance into the study was based on the results from a standardized neurological examination including radiography, serum S. neurona IgG level determination by Western Blot (WB), and a positive cerebrospinal fluid (CSF) for S. neurona IgG level by WB.

Response to treatment was determined by the investigator to be acceptable when a clinical improvement of at least one grade occurred by no later than 3 months after treatment, regardless of whether the CSF by WB was positive or negative.

Changes in clinical condition were evaluated first by the subjective scoring of the investigator, then by masked assessment of videotapes of the neurological examination. At 5 mg/kg for 28 days, 28 of 47 horses (60%) improved at least one grade by Day 118. Seventy-five percent (75%) of those improved, that had also been videotaped, were corroborated successes by videotape assessment. At 10 mg/kg, 32 of 55 animals (58%) improved at least one grade by Day 118 and 56% of those improved, that had also been videotaped, were corroborated successes using videotape assessment. With respect to the clinical investigators' scores there was no statistical difference between 5 mg/kg and 10 mg/kg treatment group results (p = 0.8867).

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

Precautions: Prior to treatment, EPM should be distinguished from other diseases that may cause ataxia in horses. Injuries or lameness may also complicate the evaluation of an animal with EPM. In most instances, ataxia due to EPM is asymmetrical and affects the hind limbs.

Neurologic deficits, primarily ataxia, have been reported to acutely worsen during the early treatment period. In some horses the worsening of the neurologic deficits was transient. (See Post Approval Experience Section).

Clinicians should recognize that clearance of the parasite by ponazuril may not completely resolve the clinical signs attributed to the natural progression of the disease. The prognosis for animals treated for EPM may be dependent upon the severity of disease and the duration of the infection prior to treatment.

The safe use of MARQUIS in horses used for breeding purposes, during pregnancy, or in lactating mares, has not been evaluated. The safety of MARQUIS with concomitant therapies in horses has not been evaluated.

Adverse Reactions: In the field study, eight animals were noted to have unusual daily observations. Two horses exhibited blisters on the nose and mouth at some point in the field study, three animals showed a skin rash or hives for up to 18 days, one animal had loose stools throughout the treatment period, one had a mild colic on one day and one animal had a seizure while on medication. The association of these reactions to treatment was not established.

Post Approval Experience (2015): The following adverse events in horses are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events have been reported:

Neurologic deficits, primarily ataxia, have been reported to acutely worsen during the early treatment period. Although outcome was not always reported, in some horses the worsening of the neurologic deficits was transient.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251.

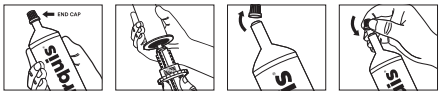
For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Animal Safety Summary: MARQUIS was administered to 24 adult horses (12 males and 12 females) in a target animal safety study. Three groups of 8 horses each received 0, 10, or 30 mg/kg (water as control, 2X and 6X for a 5 mg/kg [2.27 mg/lb] dose). Horses were dosed after feeding. One half of each group was treated for 28 days and the other half for 56 days followed by necropsy upon termination of treatment. There were several instances of loose feces in all animals in the study irrespective of treatment, sporadic inappetence and one horse at 10 mg/kg (2X) lost weight while on test. Loose feces were treatment related. Histopathological findings included moderate edema in the uterine epithelium of three of the four females in the 6X group (two treated for 28 days and one for 56 days).

Dosage: Administer MARQUIS at a dose of 15 mg/kg (6.81 mg/lb) body weight as a loading dose for the first dose only. The loading dose is followed by a maintenance dose of 5 mg/kg (2.27 mg/lb) body weight once daily for a period of 27 additional days.

Day 1: Administer a loading dose of 15 mg/kg (three times the maintenance dose) once by mouth. Because the dosage ring is calibrated by weight for the maintenance dose (5mg/kg), adjust the dosage ring to the appropriate weight and administer this 5 mg/kg dose orally, three consecutive times for a total dose of 15 mg/kg.

Day 2 through 28: Administer the maintenance dose of 5 mg/kg once daily by mouth.



Assembling: Before administration, the syringe barrel and plunger require assembly. Ensure plunger is clean and dry.

1. End cap must be on syringe barrel when inserting plunger.
2. Carefully insert plunger into base of syringe barrel until it snaps into place, then remove end cap and gently apply pressure to the plunger until paste is seen at the tip of the syringe barrel.
3. Return end cap to tip of paste syringe.

Administering MARQUIS to the horse:

Note: The paste syringe is a multi-dose package. Ensure that the correct dose is administered with each use. For the first dose only, complete steps 3 through 6 three times, then continue with steps 7 and 8.

1. Remove end cap and gently apply pressure to the plunger until paste is seen at the tip of the syringe barrel. Return end cap to tip of paste syringe.

2. Determine weight of horse and ensure the horse's mouth contains no feed.

3. To measure dose, dosage ring collar and barrel collar should be flush. Hold plunger and rotate dosage ring with the other hand to the weight of the horse.

4. Remove end cap from tip of syringe barrel.

5. The selected dose of paste should be deposited onto the back and top of the horse's tongue. Introduce tip of paste syringe into the side of the horse's mouth at the space between the front (incisor) and back (molar) teeth. Deposit paste on the horse's tongue by depressing the plunger of the syringe as far as the dose ring permits. Remove tip of syringe from horse's mouth.

6. To aid swallowing of paste, immediately raise horse's head for a few seconds after dosing.

7. Clean the tip of the syringe with a clean disposable towel and return end cap to tip of syringe barrel.

8. For the next daily dose, repeat steps 1-7.

Note: At the end of the prescribed treatment period, partially used syringes should be discarded.

Storage: Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).

How supplied:

Code: 86830183 Carton contains one (1) X 127 gram syringe applicator and one (1) syringe plunger.

Code: 86830191 Carton contains four (4) X 127 gram syringe applicators and four (4) syringe plungers.

Marketed by: Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

References:

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