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2002
A ROUNDTABLE DISCUSSION
On Recent Clinical Experience With Marquis®

Marquis®
(15% w/w ponazuril)
Antiprotozoal Oral Paste

THE FIRST APPROVED TREATMENT FOR EPM.

PARTICIPANTS

Martin Furr, DVM, DACVIM, Ph.D.
Dr. Furr earned his veterinary degree from Oklahoma State University. His residency in Large Animal Internal Medicine was completed at the Marion duPont Scott Equine Medical Center in Leesburg, Virginia, where he is currently an Associate Professor of Equine Internal Medicine. His area of interest and research includes equine neurology.

T. Douglas Byars, DVM, DACVIM, DAVECC
Dr. Byars received his veterinary degree from the University of California, Davis. He was Associate Professor of Large Animal Medicine at the University of Georgia for several years. Currently he is Hospital Director at Hagyard, Davidson, McGee Associates, PSC in Lexington, Kentucky.

Stephen M. Reed, DVM, DACVIM
Dr. Reed earned his veterinary degree from Ohio State University where he is currently Professor of Equine Internal Medicine. He is the author of over 60 articles, book chapters and abstracts. His primary research interests include cervical vertebral stenotic myelopathy and its association with osteochondroses and equine protozoal myeloencephalitis.

Bonnie S. Barr, VMD
Dr. Barr earned her veterinary degree at the University of Pennsylvania's New Bolton Center. After a one-year internship at Rood and Riddle Equine Hospital in Lexington, Kentucky, and a two-year residency at New Bolton Center, she became a staff member at Texas A&M University. She rejoined Rood and Riddle Equine Hospital as a staff veterinarian specializing in internal medicine.

Stephen Russell, DVM
Dr. Russell received his veterinary degree, magna cum laude, from Texas A&M University. He completed a large animal internship at Oklahoma State University before returning to Texas where he started his practice in Stephenville. His major interest is in equine lameness, but he also spends an equal amount of time with general medicine and reproduction.

Equine protozoal myeloencephalitis is a serious and sometimes fatal neurologic disease of horses. The disease was first recognized in the mid-1960s and a causative organism was identified in 1974 as a toxoplasma-like organism. In 1991, the organism was identified and named *Sarcocystis neurona*. Determining if it is likely that a horse has EPM prior to initiating treatment is critical for the long-term prognosis of the case.

In 2001, Marquis® (ponazuril) received approval from the Food and Drug Administration as the first drug to treat EPM. In this roundtable, equine clinicians discuss diagnosis of EPM and their experiences in treating this commonly diagnosed neurological condition in horses.

Question:

Martin Furr: What is your diagnostic plan for a horse you suspect has EPM?

Doug Byars: The clinical examination is the primary diagnostic criteria we use today. We also run serum titers, looking for horses in which clinically we suspect EPM, but that are negative or intermediate on titers. We do not collect cerebral spinal fluid (CSF) for testing, unless we feel that the differential diagnosis for something other than EPM is higher.

Question:

Furr: What clinical signs do you consider to be the most compelling for a diagnosis of EPM?

Byars: I think EPM can look like anything it wants to look like. However, if we see asymmetrical muscle atrophy, as well as upper and lower motor neuron signs, which are also asymmetrical to the limbs, we suspect EPM.

Stephen Reed: Our diagnostic criteria are very similar. We also think the neurologic exam is very critical. We see symmetric ataxia frequently, probably more than asymmetric ataxia. It's not uncommon for us to see some cranial nerve signs. In particular, we get a number of horses with dysphagia. We will almost always take cervical radiographs of suspected horses and evaluate sagittal ratios to eliminate cervical vertebral stenosis. We still collect CSF when the horses are in our hospital. We also use the Western Blot as a screening tool for horses we think are negative for EPM because horses without EPM will almost always have negative test results.

A standardized neurologic scale can be used to evaluate severity of disease and can be used to assess improvement after treatment.

Grade	Description
Grade 0	No deficits
Grade 1	Detected at a normal gait, but worsened by backing, turning, loin pressure, or neck extension
Grade 2	Deficit easily detected at normal gait and exaggerated by backing, turning, swaying, loin pressure and neck extension
Grade 3	Deficit very prominent on walking with a tendency to buckle or fall with backing, turning, loin pressure, or neck extension
Grade 4	Stumbling, tripping, and falling spontaneously
Grade 5	Horse recumbent

Bonnie Barr: Along with the neurologic exam, we will usually make sure there is no evidence of a musculoskeletal disorder. We also rely on cervical radiographs and evaluate the sagittal ratio. In addition, we often do myelograms on our patients, in which case we have CSF to evaluate.

Stephen Russell: I rely almost exclusively on clinical signs and may conduct a Western Blot or serum. I rarely collect CSF for evaluation anymore.

Furr: I think most people have recognized the problems there are in interpreting Western Blots on spinal fluid. Currently, it is common for treatment of EPM to be based primarily on clinical signs and the clinician's opinion. At our practice, we generally do spinal radiographs as part of the work-up. I usually offer to collect CSF for the sake of completeness. The one place where I think it might be more important to collect CSF is when we suspect there might be a problem other than EPM. Here on the East Coast, we are seeing cases of West Nile Virus. Any of the encephalitides would certainly be a mitigating factor for the collection of CSF.

Byars: We get a better therapeutic response in acute cases, even in cases that have severe clinical signs, than in the horse that has had clinical signs for a long time.

Question:

Furr: Do you believe the duration or the severity of the clinical signs you observe are any sort of guide in your prognosis or make a difference in the prognosis?

Russell: I'd rather treat an acute case. Even a severe acute case seems to respond better than those with marginal signs. A lot of horses with marginal signs do not seem to improve very much. In addition, if the duration of clinical signs has been very long, response seems poor.

Question:

Furr: In other words, you think that the shorter the duration of the clinical signs, the better response?

Russell: Yes, I get a better response in those patients.

Barr: I would agree that I would rather treat an acute case, than a horse that has had clinical signs for a long time. The severity of clinical signs does impact my prognosis. If I have a case that I evaluate at a Grade 4, or it is recumbent, the prognosis is much worse.

Byars: We get a better therapeutic response in acute cases, even in cases that have severe clinical signs, than in the horse that has had clinical signs for a long time. I think we are picking up a lot of performance horses earlier, which means we are able to treat them more effectively now that we are basing our diagnostics on the neurologic exam rather than just collecting and testing the CSF.

Furr: In my experience, horses that have brain stem signs are probably the ones that have the poorest response to treatment.

Reed: When they have cranial nerve deficits or other brain stem signs, it does worry me. Although not a lot of the horses present with cranial nerve deficits as their primary clinical sign, it never surprises me to have horses with EPM develop them. It may be at presentation or it may be later. The most common clinical sign is dysphagia. I would certainly agree with you that once they are starting to show brain stem signs, the prognosis is much more guarded. I also agree that the acute cases are less intimidating.

Question:

Furr: What do you think is the best horse to treat for EPM? Is it the case that gives you the most opportunities for positive prognosis?

Barr: I would say the case in which clinical signs have been recently recognized, and are not too severe – maybe a Grade 3 or so. Also, the case in which all other possibilities such as musculoskeletal problems and cervical compressive myelopathy have been ruled out.

Byars: At our practice, we do see a lot of dysphagia and facial paralysis and other signs associated with EPM. In my opinion, those horses have a greater tendency to plateau therapeutically. If they are acute, I think they respond very well. However, they may be protracted cases as far as treatment is concerned. When they plateau you recognize the limit of the treatment regimen.

Furr: I see fewer cases with cranial nerve signs than certainly some investigators report. When you see those particular signs, the horses tend not to do as well, in my hands, at least.

Question:

Furr: Dr. Russell, can you describe for us your protocol for using Marquis® (ponazuril) in the treatment of EPM?

Russell: I follow the label directions. I have not had any reason to treat them any other way. I see a good response with Marquis. Occasionally, I will use dimethyl sulfoxide (DMSO) or anti-inflammatories as adjuvant therapies.

Question:

Furr: When do you generally see a response after the initiation of treatment?

Russell: In some of the severe cases, we have seen the horses worsen for the first two or three days. After that, we see a pretty fast response, usually within a week.

Reed: It is unusual for us to see the so-called treatment crisis.

Byars: Once in a great while I have seen the horses get worse after the start of treatment. More commonly, we may see a worsening about six weeks after starting therapy with the older conventional treatments.

Furr: I think that is similar to my own experience. I rarely see a case getting worse in the first week or so. The improvement within a week is certainly consistent with what we observed in the field efficacy studies. Clients would report that they thought things were starting to improve at that point.

Reed: We start all of them off on the treatment as described (Marquis, 5 mg/kg). In any of the horses that have acute and significant neurologic signs (Grade 3 or above), we will also administer intravenous DMSO or oral DMSO. If, by the fourth week, the horse is still showing substantial clinical signs, I will administer one more week's worth of treatment. There are others that, within two weeks of the treatment ending, have a return of clinical signs. I will put them back on treatment for two to four more weeks.

Byars: We re-examine the horse 30 days after the start of treatment. At that time, we assess whether the horse is asymptomatic, its clinical signs have reached a plateau, or it is not responding. If we have been successful with the first 28 days of treatment, we stop medication, but have them come back in another 30 days for evaluation.

Barr: My treatment protocol is no different from what the others have described. We usually start with the 28-day treatment of Marquis at 5 mg/kg.

I find it is sometimes hard to decide when to stop treatment. I usually feel comfortable stopping treatment after the initial 28 days when I see an improvement in their clinical signs, and feel that the horse can return to whatever function it had in life. After 28 days, if the owner and I are not happy with the improvement, I sometimes continue treatment for another 28 days.

Barr: I usually feel comfortable stopping treatment after the initial 28 days when I see an improvement in their clinical signs, and feel that the horse can return to whatever function it had in life.

Reed: I have excellent response to a second treatment period. I cannot remember a horse we put on for a second 28 days that did not respond.

Furr: We have a similar protocol in that we treat the horse with Marquis for 28 days and schedule a recheck. After that, we make a decision on whether to continue treatment. In the efficacy trial, a lot of horses were not 100% at 28 days, but when we looked at them 90 days later, they had continued to improve. Not all of them did, but that is something that can happen. Of course, if there is a setback, we'll go back on treatment.

Question:

Furr: Because of the potential of a treatment crisis, some veterinarians have recommended horses be given some sort of non-steroidal anti-inflammatory as a routine prophylactic. Does anybody here advocate the use of that?

Russell: I don't use anti-inflammatories prophylactically in the majority of horses I treat. However, I will on some of the severe cases.

Question:

Furr: How do you define a relapse, and how often do you think you see relapse occur?

Byars: I consider it a relapse when improvement is achieved, and then clinical signs recur two to four weeks after stopping treatment. We don't see many relapses, but I think that follow-up at 30 days and again at 60 days is very important. We need to realize that the management of the horse is changing.

For example, let's say you have a performance horse that was a Grade 2 that has responded well to treatment. At 30 days, we recommend they start rehabilitation with jogs. After a 30-day period, we will reassess, and the horse may go back on medication if we are not comfortable with his progress. For the horse that hasn't shown sufficient progress in 30 days, we continue with the treatment. It seems to me that these horses tend to respond better with the second round of treatment.

Barr: We also believe it is important to either conduct a recheck at 30 days or let the referring veterinarian do it. We then decide whether or not to continue treatment.

Question:

Furr: Dr. Russell, do you have any sense for how many relapses you see in your practice?

Russell: We don't see very many. If they do relapse, I seem to have a hard time getting them to respond to treatment.

Barr: I have not seen many relapses either.

Reed: We have had two horses that I think have relapsed. I consider it a relapse when clinical signs return within one to four weeks following cessation of treatment. One of the features that represents progression of the disease is identification of new signs in another portion of the central nervous system, such as onset of cranial nerve deficits in a horse that originally demonstrated signs of spinal cord disease only.

Once a horse is returned to work or training and appears to show a worsening of its gait deficits, it behooves the veterinarian to perform both a careful and complete neurological, as well as a musculoskeletal, examination to rule out lameness as the cause of the gait deficits.

Question:

Furr: Ancillary treatments have already been mentioned. These include DMSO and other non-steroidal anti-inflammatories. Do you routinely use these or other ancillary treatments? What do you use, and how do you choose the cases in which to use them?

Byars: Vitamin E is one of the ancillary treatments we recommend because of the work done at Cornell in nerve healing. We use it in selective cases. An adult horse will receive anywhere from 10,000 to 15,000 International Units, without the selenium, per day. The length of treatment is dependent upon the clinical signs. The acute severe cases will be treated early with the ancillary DMSO, NSAIDs and steroids in some cases. When they go home, they'll be on the EPM treatment and Vitamin E for a long period of time.

Question:

Furr: In your work-up, do you ever routinely assay serum Vitamin E levels?

Reed: We do at Ohio State. We do find some low Vitamin E levels, but not too many. We still administer it to most of our neurologic cases. We give 5,000 to 8,000 International Units per day.

Barr: Depending upon the severity and the acuteness of the case, I will go with anti-inflammatories such as DMSO, phenylbutazone or flunixin meglumine. I will also put the horse on some Vitamin E. I don't send all of my neurologic cases home on Vitamin E, but if they are severe, I often do.

Depending upon on how severe the case is, I will occassionaly use steroids for a couple of days.

Question:

Furr: What steroid and dose do you usually use?

Barr: I will usually use dexamethasone, and depending upon the severity, start them off with about 60 milligrams. I gradually reduce the dose over a couple of days.

Question:

Furr: I think the ancillary treatments we have talked about are pretty routine and commonly used. There are other ancillary treatments that have been suggested – acupuncture, herbals, gold salts, algae, Thyroid Stimulating Hormone. The list is quite long. Do any of you ever include any of these?

Byars: If we get the horse to the point that he is doing well, but not well enough, and the client is interested in acupuncture, we recommend it. We have veterinarians in our practice that are acupuncturists. There have been some people who have made some claims that horses have responded to acupuncture, at least temporarily. We will tell them that it is an adjunct situation that may provide some temporary assistance.

Question:

Furr: What about tetracycline and doxycycline? These have enjoyed the support of some over the years. Has anybody used these drugs? Does anybody have an opinion on the efficacy?

Russell: I have used tetracycline, but I can't say that it helped alleviate clinical signs.

Reed: I cannot remember a horse that we have administered tetracycline to as a part of treatment. I am sure there are some in our case files; I just do not remember them. They must be infrequent.

Question:

Furr: I have certainly had cases referred to me in which tetracycline had been used and no response was seen. I think the available research data on those drugs and their action in the central nervous system would conclusively suggest that they are not going to do much. There have been people in the past that have advocated their use. Another very common adjunctive treatment is the use of various immune modulators. Does anybody have any experience with or comments on these drugs?

Barr: I have used levamisole in a couple of cases that responded well to treatment. We were also treating the horse with other medications, so I don't know whether the levamisole had a role or not.

Byars: Some of the early evidence or confusion with the diagnostic testing itself emphasized that perhaps an immune reaction to the parasite is involved in the disease. So, whether or not immune modulators would be indicated or contraindicated, would be worthy of thought.

Furr: I believe an immune reaction is a part of the pathology. In fact, in experimental models, where they try to induce EPM, the use of corticosteroids actually seems to diminish the severity of the pathology, at least in the short-term. I am sure there are some complexities of the immune response and unique features of the central nervous system environment that are mediating its response.

Question:

Furr: We have discussed a variety of treatment options and made comments on a variety of drugs that have been used in the past. How do you compare ponazuril to your previous experience with other drugs and particularly sulfa/pyrimethamine?

Byars: We've had the conventional pyrimethamine and potentiated sulfas for 20 years, so our long-term experience is with them. The shorter treatment time and our clinical involvement in both the 30-day assessment and the relapse assessment are attracting more clients to Marquis.

Reed: We were very happy and satisfied for many years with pyrimethamine and sulfadiazine. What I really like about Marquis is the ability to offer the owner a drug that we know is efficacious, based on the testing that has been done. Plus we know it will it work in a 28-day course of treatment in the majority of the cases. With pyrimethamine and sulfadiazine, 90 days is going to be a minimum treatment length and, with many horses, it may be 120 to 150 days. That is a lot of time out of somebody's life to administer medication to the horse every day. It makes it easy to recommend Marquis.

Russell: I think compliance is much better with Marquis. To me, that makes all the difference in the world. Plus, the liability issue of the compounded products concerns me. The guaranteed label of Marquis provides assurance of quality and consistency. It is nice to have a company stand behind you and to know exactly what you are administering to the horse.

Question:

Furr: So you are concerned about the quality assurance of compounded products versus a labeled product that has FDA assurance behind it?

Russell: Yes, exactly. With Marquis, I know I have a company that is standing behind the manufacturing and testing of the drug.

Barr: At our practice, we are using Marquis. Sometimes cost can be an issue for the cases that are treated with sulfa/pyrimethamine long-term. The owners are more compliant to administer Marquis, which takes less time.

Furr: Looking at the economics, a 120-day course of sulfa and pyrimethamine is going to be an equivalent cost for the drugs. And, if you treat with one 28-day course of Marquis, which is what most of my patients are on, in the long run, my clients have probably spent less on medication than they would with sulfa and pyrimethamine.

Russell: The guaranteed label of Marquis provides assurance of quality and consistency. It is nice to have a company stand behind you and to know exactly what you are administering to the horse.

The safe use of this product in horses used in breeding purposes, during pregnancy and in lactating mares has not been determined.

Question:

Furr: Another concern that I have is toxicity, which is something that we certainly see with sulfa an pyrimethamine. The toxicity of these compounds limits their use in certain cases. Does anybody else have a comment about that?

Byars: For us, the toxicity issue is a major concern because we are in a predominantly broodmare practice. The third trimester is still a question mark with any medication, but we know it is a problem with the potentiated sulfa and pyrimethamine.

Question:

Furr: I used sulfa and pyrimethamine for many years when that was the only choice. Doing a clinician-based comparison of the two drugs, I feel like I get somewhat better results with Marquis than sulfa and pyrimethamine. Does anybody else have that opinion? What is your overall success rate comparison between sulfa/pyrimethamine and ponazuril?

Russell: Marquis appears to be a lot more successful than my early years of treatment with sulfa/pyrimethamine. In the last few years, I have not had the success with sulfa/pyrimethamine that I had previously. Some of that may be due to compliance. People do not follow through with treatment with sulfa/pyrimethamine because it is such a long treatment course.

Furr: Another downside of sulfa/pyrimethamine is the recommendation of feed withdrawal before and after dosing. It is often difficult for clients to comply with this regimen.

Reed: The number one reason I use Marquis is the fact that it works. The 28-day treatment period is fantastic. Another important reason is happy clients. Marquis distinctly saves money for the owner, and it is rapid and easy to give. I am just really happy with the product. Marquis has become the only treatment in our hospital for horses with suspected EPM.

Furr: Marquis is certainly my first-line drug. It is what I routinely use. Dr. Reed mentioned what he considers to be benefits of the drug, which I agree with — convenience, short duration, solid efficacy, and the comfort that comes with a label.

Question:

Furr: One of the things that was noticeable about Marquis in its development was the safety of the drug. Dr. Barr, have you noticed any toxicity issues or any problems or complaints from owners with the use of this compound?

Barr: I have not had any complaints from owners. When the drug first came out, the first case I treated in the clinic ended up having some oral lesions, but I continued the horse on the medication and their lesions resolved. That is the only problem that I have seen with the drug.

Reed: We had two horses with hives, although during the clinical trials, I never saw any of those complicating factors that were described as evidence of toxicity.

Furr: We had about 102 horses in the safety phase of the efficacy study and two horses were reported to have hives. Both of them had hives prior to the drug being administered, as well as after it had been withdrawn. Any direct correlation between the drug and the symptoms is pretty questionable.

Question:

Furr: Does anyone have comments about how the drug is administered? The animals, in my experience, seem to take the drug pretty well and they retain it in their mouth.

Barr: If it were a top dressing, I would worry about whether the horse was going to eat it. Then, I would worry whether the animal is going to get all of the drug. I feel more comfortable with the paste. You know you got it in their mouth and unless they spit it out, you know they are going to get the recommended dose that they need.

Reed: I find it is helpful to have somebody show the owner how to administer the product. It is not that difficult, but they need to get a feel for it.

Question:

Furr: In your experience, what are the benefits of using Marquis, compared to the other treatment choices that might be out there?

Russell: Compliance of the owner is certainly a big benefit of Marquis. It also has much shorter treatment period than sulfa and pyrimethamine. It is just a better product. I really like it and my clients like it, and it works.

Question:

Furr: Is it, at this point, your first-line drug for EPM?

Russell: Yes. Definitely.

Barr: Marquis is my first-line drug for EPM. The owners are much happier to give a drug for 28 days than for several months. With the sulfas, I also worry about possible toxicity issues. I have been very happy with Marquis; therefore, it is the drug that I have been using solely.

Reed: At Ohio State, Marquis is our first drug of choice for treatment for all of the reasons mentioned. We know it is going to work. We were part of the original efficacy trials, so we feel comfortable with it. Another benefit is the convenience. The cost of Marquis is not prohibitive and certainly comparable when you are administering treatment for 90-120 days with sulfa/pyrimethamine.

Suggested Readings:

Diagnosing Equine Protozoal Myeloencephalitis. *Vet Exchange* (Suppl to *Compend Cont Ed Pract Vet* 22); 2000.

Ponazuril: Treatment for Equine Protozoal Myeloencephalitis. Clinical Advances (Suppl to *Compend Cont Ed Pract Vet* 23); 2001.

Furr M, Kennedy T, MacKay R, et al. Efficacy of Ponazuril 15% Oral Paste as a Treatment for Equine Protozoal Myeloencephalitis. *Veterinary Therapeutics*, Vol. 2, No. 3, Summer 2001.

Kennedy T, Campbell J, Selzer V. Safety of Ponazuril 15% Oral Paste in Horses. *Veterinary Therapeutics* Vol. 2, No. 3, Summer 2001.

Marquis™

(15% w/w ponazuril)

Antiprotozoal Oral Paste

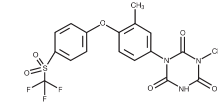
Caution: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

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 ready-to-use syringes containing 127 grams of paste. Each gram of paste contains 150 mg of ponazuril (15% w/w). Marquis (ponazuril) is designed to be delivered as an orally administered paste.

Each syringe barrel of Marquis (ponazuril) 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. 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 barrels are packaged in units of four with one reusable plunger. This package provides sufficient paste to treat one 1,200 lb (544 kg) horse for 28 days at a dose rate of 5 mg/kg (2.27 mg/lb) body weight.

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]-(9Cl)

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.

INDICATIONS: Marquis (ponazuril) 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 ($p = 0.8867$).

WARNING: For use in animals only. Not for use in horses intended for food. Not for human use. Keep out of the reach of children.

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.

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 (ponazuril) in horses used for breeding purposes, during pregnancy, or in lactating mares, has not been evaluated. The safety of Marquis (ponazuril) 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.

ANIMAL SAFETY SUMMARY: Marquis (ponazuril) 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).

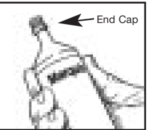
For a copy of the Material Safety Data Sheet (MSDS) or to report Adverse Reactions, call Bayer Customer Service at (800) 633-3796.

DOSAGE: Marquis (ponazuril) is to be used at a dose of 5 mg/kg (2.27 mg/lb) body weight once daily for a period of 28 days.

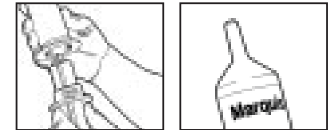
ADMINISTRATION:

Paste syringe assembly:

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



Step 1. End cap **must** be on syringe barrel when inserting plunger.



Step 2. Carefully insert reusable 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.

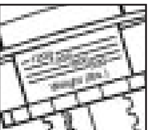
Step 3. Return end cap to tip of paste syringe.

Administering Marquis (ponazuril) to the horse:

NOTE: The paste syringe is a multi-dose package. Ensure that the correct dose is administered with each use.

Step 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.

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

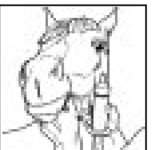


Step 3. To measure dose, dosage ring collar and barrel collar should be flush. Hold plunger and rotate dosage ring with the other hand to the weight of the horse.

Step 4. Remove end cap from tip of syringe barrel.

Step 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.

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



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

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

NOTE: When the paste syringe barrel is empty, **remove plunger for re-use and assembly with a new syringe barrel.** When removed, the plunger may retain a seal from the empty paste syringe barrel. If this occurs, remove the seal before plunger is inserted into the base of the new paste syringe barrel. At the end of the prescribed treatment period, partially used syringes should be discarded.

STORAGE: Store at Controlled Room Temperature 15-30º C (59-86º F).

HOW SUPPLIED:
Code: 045799 Carton contains four (4) x 127 gram syringe applicators and one (1) reusable syringe plunger

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Shawnee Mission, Kansas 66201 U.S.A.

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Marquis®
(15% w/w ponazuril)
Antiprotozoal Oral Paste

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