**MARQUIS®**

(15% w/w ponazuril)

Antiprotozoal Oral Paste

**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), and 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 dose of 15 mg/kg (8.81 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 dosing ring calibrated at 5 mg/kg (2.27 mg/lb) body weight and marked for horses of 500 to 1,200 lbs (227 to 544 kg). The syringe barrel is packaged with a reusable plunger. The syringe barrels are in a 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 a treatment range 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 once daily for a period of 7 additional days.

**CLINICAL PHARMACOLOGY:**

The activity of ponazuril has been demonstrated in several Apicomplexans. Lindsay, Dubey and Kennedy showed that the concentration of Sarcocystis neurona in vitro was 0.1 to 1.8 μg/mL. Furr and Kennedy evaluated the pharmacokinetics of ponazuril in serum and CSF in normal horses treated daily at 5 mg/kg (2.27 mg/lb) for 28 days. At peak serum concentrations (Cmax), ponazuril was 4.85 (±0.45) μg/mL and the maximum serum concentration (Cmax) was 5.59 (±0.92) μg/mL. The terminal elimination half-life for serum was calculated using Day 28 to 42 data was 4.50 (±0.57) days. In CSF, Cmax was 1.49 (±0.78) μg/mL and C1/2 was 0.41 (±0.07) μg/mL. A pharmacokinetic study was conducted in eight horses to compare 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 course 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 (8.81 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. The study was conducted using historical controls. In this study, each animal’s response to treatment was compared to its pre-treatment value. 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, kien pressure or neck extension
- 3: Deficit very prominent on walking, turning, lain 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.

Changes in clinical condition were evaluated first by the subjective scoring of the investigator, then by masked assessment using a standardized neurologic examination including radiography, cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG), and cerebrospinal fluid (CSF) level determination by Western Blot (WB), and a positive cerebrospinal fluid (CSF) for S. neurona IgG level determination. The study was designed to be a randomized, double-blind, placebo-controlled, 2×2 factorial treatment group, with 5 mg/kg (2.27 mg/lb) body weight and 10 mg/kg (4.54 mg/lb) body weight treatment groups. The appropriate weight and dosage ring is calibrated by weight for the maintenance dose (10 mg/kg) once daily for a period of 7 additional days.

**NOTE:**

The paste syringe is a multi-dose package. Ensure that the correct dose is administered with each use of the paste syringe. The paste syringe should be cleaned and washed thoroughly after each use. The paste syringe should be discarded after use.

**HOW SUPPLIED:**

**MARQUIS® Antiprotozoal Oral Paste**

- Code: 84672831 Carton contains one (1) x 127 gram syringe applicator and four (4) resealable plastic caps for shelf life protection.
- Code: 84672866 Carton contains four (4) x 127 gram syringe applicators and four (4) resealable plastic caps for shelf life protection.

**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 control, 2X) and 6X for a 5 mg/kg (2.87 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 noappetence and one (1) 15 mg/kg (6.81 mg/lb) lost weight while on test. Loose feces were treatment related. Histopathological findings included moderate exfolia in the uterine epithelium of three of the six horses in the 6X group (two treated for 28 days and one for 56 days).

**DOSEAGE:**

Administer MARQUIS® at a dose of 15 mg/kg (8.81 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 7 additional days.

**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, and 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.

**WARNING:**


**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 collection of the parasite by ponazuril may not completely resolve the clinical signs attributed to the natural progression of the disease. For purposes of adverse events for EP can be dependent upon the severity of the 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.

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**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 relationship if an adverse event is reported. 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 Material Safety Data Sheet (MSDS), contact Merial 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 http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation.