Date of Approval: May 21, 2015

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-188

MARQUIS

(ponazuril)

Oral Paste

Horses

Effect of Supplement: To revise the dosage regimen to include a loading dose on the first day of treatment

Sponsored by:

Merial, Inc

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I. GENERAL INFORMATION

A. File Number

NADA 141-188

B. Sponsor

Merial, Inc.
3239 Satellite Blvd.
Bldg. 500
Duluth, GA 30096-4640

Drug Labeler Code: 050604

C. Proprietary Name

MARQUIS

D. Established Name

Ponazuril

E. Pharmacological Category

Antiprotozoal

F. Dosage Form

Oral Paste

G. Amount of Active Ingredient

Each gram of paste contains 150 mg of ponazuril (15% w/w).

H. How Supplied

Carton contains one (1) X 127 gram syringe applicator and one (1) reusable syringe plunger.

Carton contains four (4) x 127 gram syringe applicators and four (4) reusable syringe plungers.

I. Dispensing Status

Rx

J. Dosage Regimen

Administer MARQUIS (ponazuril) 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.

K. Route of Administration

Oral

L. Species/Class

Horses

M. Indication

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

N. Effect of Supplement

This supplement revises the dosage regimen to include a loading dose on the first day of treatment.

II. EFFECTIVENESS

A. Dosage Characterization

Drugs with a long terminal elimination half-life (T½), such as MARQUIS (ponazuril) oral paste, require several days of administration to achieve steady state systemic drug concentrations. When rapid achievement of steady state is desirable, the administration of an initial loading dose can be appropriate.

Justification for a 15 mg/kg loading dose of MARQUIS was obtained through the analysis of a single dose study of the ponazuril pharmacokinetics (PK) in eight healthy horses (Bayer Animal Health Study no. 152.521). Eight horses (4M/4F) were dosed with MARQUIS at 5 mg/kg body weight. Post-dose serum and cerebrospinal fluid (CSF) samples were collected and the quantified results fit separately to one-compartment open models with extravascular input and first-order elimination using (Phoenix WinNonlin). Mean estimated parameter values were then used to predict the serum accumulation ratio (AR) associated with daily ponazuril concentrations for each of the eight horses. Based upon a one-compartment open body model, AR was estimated as follows:

$$\frac{1}{1-\exp^{-\lambda \times \tau}}$$

where λ = the terminal slope of the Ln-concentration/time profile and τ = dosing interval (q24h). The resulting mean, percent coefficient of variation (%CV) AR was 2.87, 12% CV (range, 2.24 to 3.31). Typically, the multiples of the daily dose needed for the loading dose is equal to the AR value. On the basis of this result analysis a 3X loading dose (15 mg/kg) was selected. Simulated serum and CSF profiles confirmed that a one-time 15 mg/kg dose allowed for steady state concentrations after one or two days of MARQUIS administration, as compared to approximately 8 days when MARQUIS is administered at a dose of 5 mg/kg once daily. Based on this information, the dosage regimen for MARQUIS can be optimized by administering a single 15 mg/kg loading dose followed by 27 additional days of treatment at the 5 mg/kg maintenance dose.

B. Substantial Evidence

The pharmacokinetic study described in the Dosage Characterization section of this FOI Summary supports the effectiveness of the 15 mg/kg loading dose. Administration of a 15 mg/kg loading dose on the first day of treatment allows MARQUIS (ponazuril) oral paste concentrations to approach steady state within 24 hours, as opposed to 8 days using the originally approved dosage regimen. The loading dose therefore provides for steady state drug exposure over the entire dosing interval. The FOI Summary for the original approval of NADA 141-188 dated July 19, 2001, contains a summary of studies that demonstrate effectiveness.

III. TARGET ANIMAL SAFETY

The pharmacokinetic study described in the Dosage Characterization section of this FOI Summary supports the safety of the 15 mg/kg loading dose. Administration of a 15 mg/kg loading dose on the first day of treatment does not result in plasma or CSF concentrations that exceed the steady state drug concentrations achieved with the dosage regimen evaluated for the original approval (5 mg/kg once daily for 28 days). The FOI Summary for the original approval of NADA 141-188 dated July 19, 2001, contains a summary of target animal safety studies.

IV. HUMAN FOOD SAFETY

This drug is intended for use in horses. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

The product labeling contains the following Warning statement:

Do not use in horses intended for human consumption.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to MARQUIS:

Not for human use. Keep out of the reach of children.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that MARQUIS, when used according to the label, is safe and effective for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

A. Marketing Status

The drug is restricted to use by or on the order of a veterinarian because professional expertise is required to diagnose EPM and to monitor safe use of this product.

B. Exclusivity

This supplemental approval for MARQUIS Oral Paste qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental application included a study of safety and effectiveness. This exclusivity begins as of the date of our approval letter and only applies to the revised dosage regimen to include a loading dose.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety and effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.