Approval Date: February 21, 2003

F R E E D O M O F I N F O R M A T I O N

S U M M A R Y

BUTEQUINE® (phenylbutazone) Paste

For relief of inflamatory conditions associated with the musculoskeletal system in horses

ANADA 200-266

Bioniche Animal Health USA, Inc.

119 Rowe Road

Athens, GA 30601

1. GENERAL INFORMATION

ANADA #: 200-266

Sponsor:
Bioniche Animal Health, Inc.
119 Rowe Road
Athens, GA, U.S.A.
30601

Trade Name: Butequine®

Established Name: Phenylbutazone Paste

Dosage Form: Oral Paste

How Supplied: 60 mL multiple dose syringes

How Dispensed: Prescription

Amount of Active Ingredient: Each calibrated plastic syringe contains 20 grams of phenylbutazone in 60 mL of paste.

Route of Administration: Oral

Species: Horses

Recommended Dosage:
1 to 2 grams of phenylbutazone per 500 lbs of body weight, but do not exceed 4 grams daily.

Guidelines to Successful Therapy:
Use a relatively high dose for the first 48 hours, then reduce gradually to a maintenance dose. Maintain lowest dose capable of producing desired clinical response. Response to Butequine therapy is prompt, usually occurring within 24 hours. If no significant clinical response is evident after 5 days, re-evaluate diagnosis and therapeutic approach.

When administering Butequine, the oral cavity should be empty. Deposit paste on back of tongue by depressing plunger that has been previously set to deliver the correct dose. Many chronic conditions will respond to Butequine therapy, but discontinuance of treatment may result in reoccurrence of symptoms.

Indications for Use:

For the relief of inflammatory conditions associated with the musculoskeletal system in horses.

Pioneer Product:
Phenylzone Paste (NADA 116-087, Schering-Plough Animal Health Corp.)

Date of Approval:

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

The effectiveness of the pioneer product was established by the National Academy of Sciences and the National Research Council (NAS/NRC) review of effectiveness. NAS/NRC determined phenylbutazone to be effective for the treatment of inflammation associated with the musculoskeletal system in the horse. The Food and Drug Administration concurred with the NAS/NRC findings. These findings were published on December 23, 1980, in 45 FR 84762.

The Center for Veterinary Medicine approved Suitability Petition number 97P-0072 CP1 on April 11, 1997. Bioniche Animal Health USA, Inc. (formerly VetrePharm Research, Inc.) requested permission to file an ANADA for Butequine® Paste which differs in strength from the pioneer product, Butazolidin® Paste (or Phenylzone® Paste) sponsored by Schering Plough Animal Health (formerly Coopers Animal Health) by the following characteristics:

Butequine® Paste: 20 grams of phenylbutazone per 60 milliliter syringe of paste (1 gram per 3 ml).

Butezolidin® Paste (or Phenylzone® Paste): 12 grams of phenylbutazone per 60-gram syringe of paste (1 gram per 5 ml).

The dosage (1-2 grams of phenylbutazone per 500 pounds body weight) is the same in both products. However, in the generic product, the dosage would be given as 3-6 milliliters per 500 lbs body weight as opposed to 5-10 milliliters of the pioneer product per 500 lbs body weight. The strengths of generic and pioneer products differ.

Bioequivalence Study:

An *in vivo* bioequivalence study was conducted to demonstrate the comparative bioavailability of Bioniche's Butequine® (test product) to the NAS/NRC reviewed standard product (Phenylzone Paste, Schering-Plough Animal Health Corp.).

Names and Addresses of Investigators

Shur-Gain Agresearch
RR#3
Burford, Ontario
N0E 1A0

Design of the Investigation

The study was designed to demonstrate the comparative bioavailability of the test product (Butequine®, Bioniche Animal Health Inc.) and the pioneer (Phenylzone Paste, Schering-Plough Animal Health Corp.).

Twenty horses (10 males and 10 females) of mixed breed were utilized in the study. The animals were randomly assigned into two groups of 10. The horses were determined to be healthy on the basis of physical examination. Feed and hay were withheld for 12 hours prior to dosing and 12 hours after dosing to minimize potential variance due to absorption of phenylbutazone to hay.

The bioequivalency study was of a crossover design. Horses of Group 1 were dosed initially with the test product and horses of Group 2 were dosed with the standard product. After a 21 day washout period, Group 1 horses received the standard product and Group 2 horses received the test product.

The standard product is available as an oral paste containing 12 grams of phenylbutazone per 60 grams of paste and the test product is an oral paste containing 20 grams of phenylbutazone per 60 mL of paste. The pastes were administered orally.

A dosage of 2 grams of phenylbutazone per 500 pounds of body weight was utilized in the study (10 grams of paste for the standard product and 6 mL of the paste for the test product). The dosage of each formulation was weighed and administered in an individual syringe of known weight. The syringe was reweighed after dosing and the residue in the syringe was calculated and subtracted from the total dosage. This was done to hold variability in dosage to a minimum.
The duration of the test for each replicate in the crossover study was 48 hours. The pertinent parameters measured included serum drug concentrations for phenylbutazone at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 18, 24, 30, 36, 48 and 60 hours after dosing and the incidence of adverse reactions. Serum samples were collected, stored frozen, and shipped frozen to the laboratory performing the analyses. The content of phenylbutazone in the samples was determined by High Performance Liquid Chromatography (HPLC). The chemist who performed the HPLC tests and calculations was unaware of the group assignments for the study.

Results

Table 1 gives the mean serum concentrations of phenylbutazone at each time period for both the test product and the standard product. Concentrations are in micrograms per milliliter.

Table 1

Time (hours)	Test Product	Standard Product
0	0.000	0.013
0.25	0.341	0.301
0.50	3.81	2.57
1	12.6	6.37
1.5	18.1	9.25
2	20.0	10.9
3	22.4	13.1
4	23.4	17.1
6	24.1	22.3
9	23.0	24.9
12	20.1	22.5
18	16.4	18.9
24	10.1	11.1
30	5.36	6.24
36	2.67	3.02
48	0.612	0.625
60	0.148	0.131

Statistical Analysis and Conclusions

The variables area under curve (AUC), maximum blood concentration (Cmax), and time to maximum concentration (Tmax) for the study were calculated and subjected to analysis of variance with the results summarized in table 2.

Table 2

Variable	Schering mean	Bioniche mean	Lower	Upper
Time to Max. Concentration	5.447	8.788	-55.89	-20.00
Area under Curve	502.30	529.11	84.33	106.87
Maximum Concentration	24.92	27.31	80.08	103.99

Using the (percentage) confidence intervals approach, the results support the claim for bioequivalence between Bioniche's product and Schering-Plough's product.

Adverse Reactions

No adverse reactions were reported during the study.

Animal Safety

Phenylbutazone paste was reviewed by the NAS/NRC and found to be safe in horses at the recommended dosages reflected on the product labeling. Findings of the NAS/NRC were published December 23, 1980 in 45 FR 84762.

3. HUMAN SAFETY:

Human Safety Relative to Food Consumption:

Regarding consumption of drug residues in food, human safety data is not required since this drug is labeled for use in horses not intended for food. The product labeling will contain the following statement:

"WARNING: Not for use in horses intended for food."

Human Safety Relative to Possession, Handling and Administration:

Labeling contains the following warning statement:

"WARNING: Keep this and all medications out of the reach of children."

4. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, And Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that BUTEQUINE™ (phenylbutazone) Paste when used under its proposed conditions of use, is safe and effective for the labeled indications.

Attachment: Generic and pioneer labeling

Generic
60 mL (20 gm) syringe and carton

Pioneer

12 gm syringe