Date of Approval: March 28, 2003

FREEDOM OF INFORMATION SUMMARY

ANADA 200-323

Indications for use: For relief of inflammatory conditions associated with the musculoskeletal system in horses.

Sponsored by:
West-Ward Pharmaceutical Corp.
465 Industrial Way West
Eatontown, NJ 07724

FREEDOM OF INFORMATION SUMMARY
ANADA 200-323

1. **GENERAL INFORMATION:**

a. File Number: ANADA 200-323

b. Sponsor: West-Ward Pharmaceutical Corp.
465 Industrial Way West
Eatontown, NJ 07724

c. Established/Name: Phenylbutazone Tablets

d. Proprietary/Name: Phenylbutazone Tablets USP, 1 gram

e. Dosage Form: Tablets

f. How Supplied: 20 Tablet bottles

g. How Dispensed ℞

h. Amounts of Active Ingredients: 1 g phenylbutazone/tablet

i. Route of Administration: Oral

j. Species/Class: Equine (horses)

k. Recommended Dosages: 2 to 4 mg/lb of body weight (equivalent to 1 to 2 grams per 500 lb of body weight) or 2 to 4 Phenylbutazone Tablets, 1g for 1000lb of body weight per day. Do not exceed 4 grams per animal per day. Administer in 3 divided daily doses. Use up to the maximum recommended dose for the first 48 hours, then reduce gradually to a maintenance dose. Maintain lowest dose capable of producing desired clinical response.

l. Pharmacological Category: Anti inflammatory

m. Indications for use: For relief of inflammatory conditions associated with the musculoskeletal system in horses.

n. Pioneer Product Dosage: NADA 99-618, Bizolin 1g tablet, Boehringer Ingelheim Vetmedica.

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

A comparative, randomized, single-dose, 2-way crossover bioavailability study of West-Ward manufactured Phenylbutazone Tablets, 1 g and Boehringer Ingelheim Vetmedica (Bizolin®) 1 g Phenylbutazone tablets in healthy adult horses following administration of an 8.8 mg/kg dose under fasting conditions was conducted.

NAME(S) AND ADDRESS(ES) OF INVESTIGATOR(S)

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Animal Phase Site
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Forkadeer Farm
Route 1, Box 145F
Pikeville, TN 37367
Telephone: 423-533-2400

GENERAL DESIGN OF INVESTIGATION

a. Purpose of Study

The objective of this study was to compare the single-dose bioavailability of West-ward and Boehringer Ingelheim Vetmedica (Bizolin®) 1 g Phenylbutazone tablets in healthy adult horses following administration of an 8.8 mg/kg dose under fasting conditions.

b. Test Animals

1. Species and number per group

A total of 26 adult horses. Twelve geldings and twelve mares were selected for the study.

2. Identify appropriate subgroups (e.g., age, sex, weight, breed or class)

Twelve geldings and twelve mares, all greater than 3 years of age, were selected for the study.

ID Number	Sex	Weight (kg)	Age (Years)
154	Male	403	3.5
156	Male	407	20
152	Male	416	10
174	Male	434	20
168	Male	444	13
172	Male	455	5
173	Female	402	7
155	Female	418	15
159	Female	443	15
161	Female	457	25
151	Female	471	10
175	Female	497	20
150	Male	389	20+
166	Male	411	4
160	Male	422	12+
164	Male	427	18
176	Male	435	8
162	Male	481	8
157	Female	385	8
177	Female	430	6
149	Female	434	25
181	Female	446	20
169	Female	471	16
163	Female	499	18

c. Type of control group used

1. Cross-over

d. Diagnosis

The AUC, AUCinf, AUC/AUCinf, Cmax, Tmax, Ke, MRT and half-life pharmacokinetic parameters were calculated for Phenylbutazone in horse plasma. The ANOVA model included sequence, treatment and period as fixed effects and animal-within-sequence as a random effect. The 90% confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the In-transformed AUC and Cmax pharmacokinetic parameters.

e. Dosage Form
Tablets

f. Route(s) of administration
Dose was administered via a balling gun administered by mouth

g. Dosage(s) used
Dose in study was 8.8 mg/kg (2g/500lb)

h. Test duration
June 26, 2000 – Begin acclimation phase. July 22, 2000 – Horses returned to herd.

i. Pertinent Parameters measured

1. Chemistry and Hematology:
A pre-treatment blood sample was taken once per animal during the acclimation phase of the study (Days -14 to Day -6).

Post-Treatment Clinical Observations Noted

ID Number	Treatment (product)	Time of Observation (hours)	Post-treatment Observation
181	West-ward	1	Drooling slightly – lower lip hanging slightly
		2	Lip still drooping, but salivation has stopped
		3	Drooping lower lip
161	Bizolin®	1	Mild salivation (thick) and protruding tongue
		2	Less salivation but tongue protrudes to left
		3	Still has protruding tongue but salivation has nearly ceased (at feeding, good appetite and no apparent problems with mastication)
163	West-ward	1	Mild salivation
		2	Frothy saliva – slight amounts
		3	Minimal amounts of frothy saliva
160	Bizolin®	2	Small amounts of frothy saliva on lips
		3	Slight salivation
149	Bizolin®	1	Mild salivation
		2	Mild salivation
176	Bizolin®	~1.5	Mild salivation
		2	Mild salivation
		3	Mild salivation
163	Bizolin®	3	Small amount of frothy saliva on lips

1. RESULTS

Summary of Results – Phenylbutazone in horse Plasma
Pharmacokinetic Parameters
(N = 24)

	ln AUC* (ng.h/mL)	ln Cmax* (ng/mL)	Tmax (h)	Ke (1/h)	MRT (h)	Half-life (h)	AUC/AUCinf (%)
West-ward (A)							
Mean	388767.77	27283.404	4.854	0.09632	14.58	7.377	94.49
CV	38.3	39.3	31.8	17.5	12.9	15.1	2.5
n	24	24	24	24	24	24	24
BIV (B)							
Mean	368213.42	27399.252	4.458	0.09470	14.83	7.531	94.24
CV	30.3	38.3	35.9	16.8	14.7	17.9	2.9
n	24	24	24	24	24	24	24
Least-Squares Means							
West-ward (A)	388767.76	27283.404					
BIV (B)	368213.43	27399.252					
Ratio of Lease-Square Means (A/B) %	105.6	99.6					
90% Confidence Intervals (A/B) %							
Lower Limit:	92.7%	84.9%					
Upper Limit:	120.3%	116.8%					
p-Value (ANOVA)							
A vs B	0.4820	0.9641					
Period	0.5861	0.7101					
Sequence	0.6846	0.2041					

* For ln-transformed parameters, the antilog of the mean (i.e., the geometric mean) is reported.
** Standard Error of the difference was obtained based on the ln-transformed data.

2. STATISTICAL ANALYSIS

Arithmetic means, standard deviations and coefficients of variation were calculated for AUC, AUCinf, AUC/AUCinf, Cmax, Tmax, Ke, MRT and half-life. Additionally, geometric means were calculated for the In-transformed parameters AUC and Cmax.

Analyses of ln-transformed AUC and Cmax were performed by analysis of variance (ANOVA) with sequence, animal-within-sequence, period and treatment terms in the ANOVA model. The sequence effect was tested against the animal-within-sequence term at the 10% level. Treatment effect was tested against the residual error at the 10% level. Least-square means (LSM) for AUC and Cmax for the two treatment groups, along with standard errors, were obtained based on the ln-transformed data. The analysis was performed by the PROC GLM procedure in SAS®.

Consistent with the two one-sided test for bioequivalence[2] (90% confidence intervals for the difference between drug formulation) LSM were calculated for the parameters AUC and Cmax, using ln-transformed data. The confidence intervals are expressed as a percentage relative to the LSM of the reference formulation.

Ratios of means were calculated using the LSM for ln-transformed AUC and Cmax. The geometric mean values were reported for ln-transformed parameters. Ratios of means are expressed as a percentage of the LSM for the reference formulation.

CONCLUSION

The ratios of least-squares means and the 90% confidence intervals for the ln-transformed parameters AUC and Cmax for Phenylbutazone were within the 80 – 125% CVM acceptance range. Based on these results, the West-ward and Boehringer Ingelheim Vetmedica (Bizolin®) 1 g Phenylbutazone tablets are bioequivalent under fasting conditions.

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: Treated animals should not be slaughtered for food."

Human Safety Relative to Possession, Handling and Administration:

Labeling contains the following warning statement:

" Keep out of the reach of children."

"For use in animals only."

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 West-Ward Phenylbutazone Tablets when used under its proposed conditions of use, is safe and effective for the labeled indications.

5. ATTACHMENTS:

Generic Labeling
20,100, and 250 tablet bottles
Package Outsert

Pioneer Labeling-Bizolin® 100 tablets/bottle