

H FA-305

Date of Approval: MAR 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**

200-323-FOIS 1

**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** R
- 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)

Animal Phase Investigator

Craig Reinemeyer, DMV, PhD
East Tennessee Clinical Research, Inc.
4315 Papermill Drive
Knoxville, TN 37909
Telephone: 865-212-0004
Fax: 865-212-0047

Animal Phase Site

Ronny and Judy Swafford, Owners
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 Least-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 ln-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 bioequivalence² (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

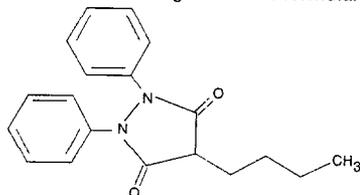
ANADA 200-323
Phenylbutazone Tablets
1 gram

Anti-inflammatory for Horses

DESCRIPTION: The clinical effectiveness of phenylbutazone in acute rheumatism, gout, gouty arthritis, and various other rheumatoid disorders in man was demonstrated by Kuzell^{1,2,3}, Payne⁴, Fleming⁵, and Denko⁶. Anti-inflammatory activity has been well-established by Fabre⁷, Domenjoz⁸, Wilhelmi⁹, and Yourish¹⁰. The effective use of phenylbutazone in the treatment of painful conditions of the musculoskeletal system in dogs, including arthritis and painful injuries to the limbs and joints has been reported by Lieberman¹¹. Joshua¹² observed objective improvement without toxicity following long-term therapy of two aged arthritic dogs. Ogilvie and Sutter¹³ reported rapid response to phenylbutazone therapy in a review of 19 clinical cases including posterior weakness, arthritis, rheumatism, and other conditions associated with lameness and musculoskeletal weakness.

Favorable results have been reported by Camberos¹⁴ following intermittent treatment of horses in generalized arthritis, chronic pain in trapezius muscles, osteoarthritis of the medial and distal bones of the hock, chronic hip pairs, arthritis of stifle and hip, arthrosis of the spine. In cases of traumatism, muscle rupture, inflammation of the third phalanx, and strains, results were less favorable. Sutter¹⁵ reported favorable response to chronic equine arthritis.

Chemically it is C₁₉H₂₀N₂O₂ (4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione) and has the following structural formula:



M.W 308.37

Each tablet also contains phenylbutazone 1 g. Inactive ingredients: Colloidal Silicon Dioxide, Corn Starch, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, and Sodium Starch Glycolate.

INDICATIONS AND USAGE: Phenylbutazone tablets have non-hormonal anti-inflammatory properties in the management of musculoskeletal conditions in horses, such as generalized arthritis.

CONTRAINDICATIONS: Animals showing evidence of cardiac, hepatic, or renal damage or a history of blood dyscrasia, or those with signs or history of anemia.

WARNING: Treated animals should not be slaughtered for food purposes.

PRECAUTIONS: Stop medication at first sign of gastrointestinal upset, blood dyscrasia, jaundice, or black or tarry stools. Agranulocytosis associated with the drug has occurred in man and was reversible upon discontinuance of treatment. Fatal reactions, although rare, have been reported in dogs after long-term therapy. Routine blood counts should be made at weekly intervals during the early phase of therapy and thereafter at intervals of two weeks. A significant fall in total white count, or a relative decrease in granulocytes, or black or tarry stools indicate that therapy with phenylbutazone tablets, 1 gram should be immediately discontinued. In the treatment of inflammatory conditions associated with infection specific anti-infective therapy is required. Caution should be observed when administering to patients with a history of drug allergy.

DOSAGE AND ADMINISTRATION: Horses: 2 to 4 mg per lb of body weight (equivalent to 1 to 2 grams per 500 lb of body weight) or 2 to 4 phenylbutazone tablets, 1g for 1000 lb of body weight per day. Do not exceed 4 grams per animal per day. As symptoms regress, reduce dosage 25% to 50% of initial dose as needed to control symptoms. If there is no improvement in 5 days discontinue treatment. Infective conditions should be treated concurrently with the proper anti-infectives. Response to treatment is variable, as is also the tolerance for the drug. Withdrawal of the drug may be followed by reappearance of symptoms, after which it may be given intermittently to control

symptoms. The drug is symptomatic in action and not curative.

RECOMMENDATIONS: Use up to the maximum recommended dose for the first 48 hours. As symptoms regress, reduce dosage 25% to 50% of the initial "loading dose" as needed to control symptoms.

Because of the more rapid metabolism in animals, administer phenylbutazone tablets in 3 divided daily doses (at 8-hour intervals) to maintain therapeutic blood level. Response to phenylbutazone tablets treatment usually occurs within 24 hours after the initial dose. If no response is evident after 5 days of dosing, treatment should be discontinued.

While many chronic conditions, such as chronic osteoarthritis, will respond to phenylbutazone therapy, no permanent cure can be effected owing to the advance tissue changes. In such cases discontinuance of treatment often will result in recurrence of symptoms. However, intermittent therapy may be extremely valuable to alleviate symptoms of chronic inflammatory lesions.

HOW SUPPLIED: Phenylbutazone Tablets, 1 g are supplied as white, round, scored tablets, embossed "WW 462" on scored side and plain on the other side.

Bottles of 20 tablets
Bottles of 100 tablets
Bottles of 250 tablets

Store at controlled room temperature, 15°-30°C (59°-86°F) [See USP].

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

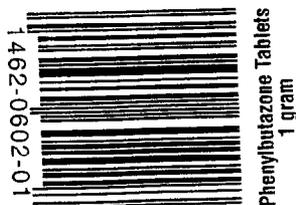
Keep out of the reach of children.

For use in animals only.

References:

1. Kuzell, W.C.; Schaffarzick, R.W.; Naugler, W. G.; and Mankle, E. A. *AMA Arch. Int. Med.* 92:646 (1953)
2. Kuzell, W.C.; Schaffarzick, R. W.; Brown, B.; and Mankle, E. A. *JAMA* 149:729 (1952)
3. Kuzell, W. C., and Schaffarzick, R. W. *Calif. Med.* 77:319 (1952)
4. Payne, R. W.; Shetlar, M. R.; Farr, C.; Hellbaum, A. A.; and Ishmael, W. K.T.J. *Lab. Clin. Med.* 45:331 (1955)
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11. Lieberman, L. L. *Jour. Amer. Vet. Med. Assoc.* 125:128 (1954)
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13. Ogilvie, F B., and Sutter, M. D. *Vet. Med.* 52:492 (1957)
14. Camberos, H. R. *Rev. Med. (Buenos Aires)* 38:9 (1956)
15. Sutter, M. D. *Vet. Med.* 58:83 (Feb., 1958)

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, NJ 07724
Issued June 2002



NDC 0143-1462-02

Phenylbutazone Tablets

1 g

Anti-inflammatory for Horses

Caution: Federal (USA) law restricts this drug to use by or on order of a licensed veterinarian.

ANADA 200-323

250 Tablets

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Store at controlled room temperature
15°-30°C (59°-86°F)

For use in animals only.

Warning: Treated animals should not be slaughtered for food purposes.



N 0143-1462-02 4

Exp. Date:
Control No.:

Each tablet contains:
Phenylbutazone..... 1 g

USUAL DOSAGE:
Horses, 1 to 2 grams per 500 lb of body weight daily,
not to exceed 4 grams daily.
See accompanying product literature
for complete information.

CCL-1

KEEP OUT OF REACH OF CHILDREN

NDC 0143-1462-02

Phenylbutazone Tablets

1 g

Anti-inflammatory for Horses

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for complete information.

CCL-1

KEEP OUT OF REACH OF CHILDREN

NDC 0143-1462-01

Phenylbutazone Tablets

1 g

Anti-inflammatory for Horses

Caution: Federal (USA) law restricts this drug to use by or on order of a licensed veterinarian.

ANADA 200-323

100 Tablets

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Store at controlled room temperature
15°-30°C (59°-86°F)
For use in animals only.

Warning: Treated animals should not be slaughtered for food purposes.



3 0 143-1462-01 7

Exp. Date:
Control No.:

KEEP OUT OF REACH OF CHILDREN

C-1

Horses: 1 to 2 grams per 500 lb of body weight daily, not to exceed 4 grams daily.
See accompanying product literature for complete information.

USUAL DOSAGE:
Phenylbutazone 1 g

Each tablet contains:
Phenylbutazone..... 1 g

NDC 0143-1462-01

Phenylbutazone Tablets

1 g

Anti-inflammatory for Horses

Caution: Federal (USA) law restricts this drug to use by or on order of a licensed veterinarian.

ANADA 200-323

100 Tablets

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Store at controlled room temperature
15°-30°C (59°-86°F)
For use in animals only.

Warning: Treated animals should not be slaughtered for food purposes.



3 0 143-1462-01 7

Exp. Date:
Control No.:

KEEP OUT OF REACH OF CHILDREN

C-1

Horses: 1 to 2 grams per 500 lb of body weight daily, not to exceed 4 grams daily.
See accompanying product literature for complete information.

USUAL DOSAGE:
Phenylbutazone..... 1 g

NDC 0143-1462-01

Phenylbutazone Tablets

1 g

Anti-inflammatory for Horses

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ANADA 200-323

100 Tablets

Manufactured by:
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Eatontown, N.J. 07724

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For use in animals only.

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3 0 143-1462-01 7

Exp. Date:
Control No.:

KEEP OUT OF REACH OF CHILDREN

C-1

Horses: 1 to 2 grams per 500 lb of body weight daily, not to exceed 4 grams daily.
See accompanying product literature for complete information.

USUAL DOSAGE:
Phenylbutazone..... 1 g

Each tablet contains:
Phenylbutazone..... 1 g

KEEP OUT OF REACH OF CHILDREN
XX-1

NDC 0143-1462-20

Phenylbutazone Tablets

Each tablet contains:
Phenylbutazone, 1 g

USUAL DOSAGE:
Horses: 1 to 2 grams per 500 lb of body weight daily, not to exceed 4 grams daily. See accompanying product literature for complete information.

Anti-inflammatory for Horses

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

ANADA 200-323

20 Tablets

Manufactured by
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Store at controlled room temperature
15°-30°C (59°-86°F) [See USP].
For use in animals only.

Warning: Treated animals should not be slaughtered for food purposes.



Exp. Date
Control No.

KEEP OUT OF REACH OF CHILDREN
XX-1

NDC 0143-1462-20

Phenylbutazone Tablets

Each tablet contains:
Phenylbutazone, 1 g

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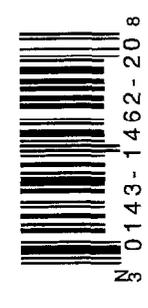
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For use in animals only.

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Exp. Date
Control No.

Lot No.:

Exp. Date:

Bizolin® - 1 g

(phenylbutazone)

1 gram per Tablet

A Brand of Phenylbutazone
Anti-inflammatory for Horses

NADA 099-618, Approved by FDA

Net Contents: 100 Tablets

Each tablet contains:

Active Ingredient: Phenylbutazone 1 gram

Inert Ingredients: (as excipients) q.s.

Dosage: Horses: 1 to 2 grams per 500 lb of body weight daily, not to exceed 4 grams daily.

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

Warning: Treated animals should not be slaughtered for food purposes. Refer to folded label attached to this container for additional information, dosage, and cautions.

Store at controlled room temperature, 59° - 86°F (15° - 30°C).

For use in animals only.

Keep out of reach of children.

Boehringer Ingelheim Vetmedica, Inc.
St. Joseph, MO 64506 U.S.A.

445103L-01-9901
Code 445111



000005

Bizolin Tablets, 1 g
(phenylbutazone)

QUANTITY	LOT NO	EXP DATE
 12 x 100's		
ITEM NUMBER		
 445111000		 10012315445114

Store at controlled room temperature 59°-86°F (15°-30°C)

Boehringer Ingelheim Vetmedica, Inc
St. Joseph, MO 64506 U.S.A

445104C-01-9902

Bizolin® Tablets

1 gram per Tablet

A Brand of Phenylbutazone
Anti-inflammatory for Horses

Each tablet contains: Active Ingredient – Phenylbutazone (4-butyl-1,2-diphenyl-3,5-pyrazolidinedione) 1 gram; inert ingredients (as excipients) – q. s.

Description: The clinical effectiveness of phenylbutazone in acute rheumatism, gout, gouty arthritis, and various other rheumatoid disorders in man was demonstrated by Kuzell^{1,2,3}, Payne⁴, Fleming⁵, and Denko⁶. Anti-inflammatory activity has been well-established by Fabre⁷, Domenjoz⁸, Wilhelm⁹, and Yourish¹⁰. The effective use of phenylbutazone in the treatment of painful conditions of the musculoskeletal system in dogs, including arthritis and painful injuries to the limbs and joints has been reported by Lieberman¹¹. Joshua¹² observed objective improvement without toxicity following long-term therapy of two aged arthritic dogs. Ogilvie and Sutter¹³ reported rapid response to phenylbutazone therapy in a review of 19 clinical cases including posterior weakness, arthritis, rheumatism, and other conditions associated with lameness and musculoskeletal weakness.

Favorable results have been reported by Camberos¹⁴ following intermittent treatment of horses in generalized arthritis, chronic pain in trapezius muscles, osteoarthritis of the medial and distal bones of the hock, chronic hip pains, arthritis of stifle and hip, arthrosis of the spine. In cases of traumatism, muscle rupture, inflammation of the third phalanx, and strains, results were less favorable. Sutter¹⁵ reported favorable response to chronic equine arthritis.

Indications: Bizolin Tablets have non-hormonal anti-inflammatory properties in the management of musculoskeletal conditions in horses, such as generalized arthritis.

Contraindications: Animals showing evidence of cardiac, hepatic, or renal damage or a history of blood dyscrasia, or those with signs or history of anemia. Treated animals should not be slaughtered for food purposes.

Precautions: Stop medication at first sign of gastrointestinal upset, blood dyscrasia, jaundice, or black or tarry stools. Agranulocytosis associated with the drug has occurred in man and was reversible upon discontinuance of treatment. Fatal reactions, although rare, have been reported in dogs after long-term therapy. Routine blood counts should be made at weekly intervals during the early phase of therapy and thereafter at intervals of two weeks. A significant fall in total white count, or a relative decrease in granulocytes, or black or tarry stools indicate that therapy with Bizolin Tablets, 1 gram should be immediately discontinued. In the treatment of inflammatory conditions associated with infection specific anti-infective therapy is required. Caution should be observed when administering to patients with a history of drug allergy.

Dosage and Administration: Horses. 2 to 4 mg per lb of body weight (equivalent to 1 to 2 grams per 500 lb of body weight) or 2 to 4 Bizolin Tablets, 1 g for 1000 lb of body weight per day. Do not exceed 4 grams per animal per day. As symptoms regress, reduce dosage 25% to 50% of initial dose as needed to control symptoms. If there is no improvement in 5 days discontinue treatment. Infective conditions should be treated concurrently with the proper anti-infectives. Response to treatment is variable, as is also the tolerance for the drug. Withdrawal of the drug may be followed by reappearance of symptoms, after which it may be given intermittently to control symptoms. The drug is symptomatic in action and not curative.

Recommendations: Use up to the maximum recommended dose for the first 48 hours. As symptoms regress, reduce dosage 25% to 50% of the initial "loading dose" as needed to control symptoms.

Because of the more rapid metabolism in animals, administer Bizolin Tablets in 3 divided daily doses (at 8-hour intervals) to maintain therapeutic blood level. Response to Bizolin Tablets treatment usually occurs within 24 hours after the initial dose. If no response is evident after 5 days of dosing, treatment should be discontinued.

While many chronic conditions, such as chronic osteoarthritis, will respond to Bizolin therapy, no permanent cure can be effected owing to

the advance tissue changes. In such cases discontinuance of treatment often will result in recurrence of symptoms. However, intermittent therapy may be extremely valuable to alleviate symptoms of chronic inflammatory lesions.

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

Warning: Treated animals should not be used for food purposes.

Store at controlled room temperature, 59°-86°F (15°-30°C).

Keep out of the reach of children.

For use in animals only

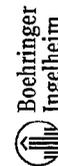
References:

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2. Kuzell, W. C., Schaffarzick, R. W., Brown, D., and Mankie, E. A. *JAMA* 149:729 (1952)
3. Kuzell, W. C., and Schaffarzick, R. W. *Calif Med* 77:319 (1952)
4. Payne, R. W., Shetlar, M. R., Farr, C.; Hellbaum, A. A., and Ishmael, W. K. T. *J. Lab. Clin. Med.* 45:351 (1955)
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6. Denko, C. W., and Ruml, D. *Amer. Practit.* 6:1865 (1955)
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13. Ogilvie, F. E., and Sutter, M. D. *Vet. Med.* 52:492 (1957)
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445103L-01-9901

Boehringer Ingelheim P.O. Box 448892

Each tablet contains:
Active ingredient: Phenylbutazone 1 gram
Inert ingredients (as excipients) q. s.
Dosage: Horses: 1 to 2 grams per 500 lb of body weight daily, not to exceed 4 grams daily
Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
Warning: Treated animals should not be slaughtered for food purposes. Treated animals should be identified to this container for additional information, dosage, and cautions.
Store at controlled room temperature, 59°-86°F (15°-30°C).
For use in animals only.
Keep out of reach of children.
Boehringer Ingelheim, Vetmedica, Inc.,
St. Joseph, MO 64506 U.S.A.
445103L-01-9901
Code 445111



Bizolin® - 1 g

(phenylbutazone)

1 gram per Tablet

A Brand of Phenylbutazone

Anti-inflammatory for Horses

NADA 099-618, Approved by FDA

Net Contents: 100 Tablets