Approval Date: February 10, 2003

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-034

GAINPRO® (bambermycins) Type A Medicated Article

"For increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, and dairy and beef replacement heifers)."

Sponsored By:

Intervet Inc.
405 State Street
Millsboro, DE 19966

Page

FREEDOM OF INFORMATION SUMMARY

GAINPRO® for Pasture Cattle

1. General Information:

a. File Number:	NADA 141-034
b. Sponsor:	Intervet Inc. 405 State Street Millsboro, DE 19966-0318 Drug Labeler Code: 057926
c. Established Name:	Bambermycins
d. Proprietary Name:	**GAINPRO®**
e. Dosage Form:	Feed
f. How Supplied:	Type A medicated article in 50 lb. multi-walled bags
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	10 grams of bambermycins per pound
i. Route of Administration:	Oral in feed
j. Species/Class:	Pasture cattle (slaughter, stocker, feeder cattle and dairy and beef replacement heifers)
k. Recommended Dosage:	Feed continuously in a free-choice or hand-fed supplemental feed to provide not less than 10 nor more than 40 mg/head/day. Daily bambermycins intakes in excess of 20 mg/head/day have not been shown to be more effective than 20 mg/head/day. For hand-fed use, the drug must be contained in at least 1 pound and not more than 10 pounds of supplemental feed.
l. Pharmacological Category:	Antibacterial
m. Indications:	For increased rate of weight gain in pasture cattle.
n. Effect of Supplement:	To provide for free-choice and hand-fed consumption of bambermycins at a rate of not less than 10 mg nor more than 40 mg per head

per day to increase rate of weight gain in pasture cattle.

2. EFFECTIVENESS

For Cattle Hand-Fed:

Summary of Efficacy Data (*As previously described in FOI Summary dated March 4, 1994 for GAINPRO® for pasture cattle (59 FR p. 15624; April 4, 1994); March 4, 1994 approval*).

Five (5) pivotal dose titration studies were conducted using a randomized complete block design and 1300 growing calves. The studies are summarized and evaluated below for significant differences in rate of weight gain. The 1300 test animals used in these five (5) pasture studies were fullbred or crossbred animals of European and exotic breeds. At three (3) study locations, there were five (5) test blocks in which each block consisted of six (6) adjacent pastures. Six (6) treatments, 0, 10, 20, 40, 60, and 80 mg bambermycins per head per day, were randomly assigned to the pastures within each block. Ten (10) steers or heifers were randomly assigned to each pasture. At two (2) study locations, there were five (5) test blocks in which each block consisted of four (4) adjacent pastures. Four (4) treatments, 0, 5, 10 and 20 mg bambermycins head per day, were randomly assigned to the pastures within each block. Ten (10) steers or heifers were randomly assigned to each pasture. Hence, at each of the five (5) study locations, each treatment tested was replicated five (5) times, and for the five (5) combined locations eighteen (18) blocks of steers and seven (7) blocks of heifers were tested. The initial animal weights ranged from 160 to 320 kgs and the studies were terminated when the animals reached 250 to 410 kgs. Feeding periods ranged from 92 to 107 days.

During the studies the cattle were rotated across pastures within a block to minimize any effect(s) of pasture conditions. Each animal received daily .45 or .90 kg of supplemental feed containing bambermycins to provide the assigned treatment dosage. Bambermycins was administered daily via hand feeding supplemental feed. The five (5) studies are summarized as follows:

Trial No. 946-17

Investigator: Robert W. Lee
KanTech Research Foundation
P.O. Box 1036
Garden City, Kansas 67846

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

This study was conducted using 300 yearling steers. The cattle were fed supplemental feed for 104 days on native buffalograss pastures. There were 10 animals per pasture and 5 replications of each treatment. The results were as follows:

	Bambermycins (mg/head/day)					
	0.0	10.0	20.0	40.0	60.0	80.0
Average Daily Gain (kg)	0.762	1.033	0.927	0.927	0.973	0.893

Trial No. 946-18

Investigator: Terry Klopfenstein
Department of Animal Science
236 Marvel Baker Hall
University of Nebraska
Lincoln, Nebraska 68583

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

This study was conducted using 120 yearling steers and 180 yearling heifers. The cattle were fed supplemental feed for 107 days on native smooth brome pastures. There were 10 animals per pasture and 5 replications of each treatment. The results were as follows:

	Bambermycins (mg/head/day)					
	0.0	10.0	20.0	40.0	60.0	80.0
Average Daily Gain (kg)	0.690	0.742	0.793	0.771	0.812	0.788

Trial No. 946-19

Investigator: Ed G. Johnson
Johnson Research
24007 Highway 20/26
Parma, Idaho 83660

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

A study was conducted using 180 yearling steers and 120 yearling heifers. The cattle were fed supplemental feed for 106 days on irrigated fescue and ladino clover pastures. There were 10 animals per pasture and 5 replications of each treatment. The results were as follows:

	Bambermycins (mg/head/day)					
	0.0	10.0	20.0	40.0	60.0	80.0
Average Daily Gain (kg)	0.777	0.773	0.842	0.843	0.863	0.856

Trial No. 946-20

Investigator: William E. Kunkle
University of Florida
231 Animal Science Building
Gainesville, Florida 32611

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

A study was conducted using 120 yearling steers and 80 yearling heifers. The cattle were fed supplemental feed for 96 days on wheat and ryegrass pastures. There were 10 animals per pasture and 5 replications of each treatment. The results were as follows:

	Bambermycins (mg/head/day)			
	0.0	5.0	10.0	20.0
Average Daily Gain (kg)	0.876	0.884	0.903	0.945

Trial No. 946-21

Investigator: William C. Ellis
Colonial Farms
704 Encinas Place
College Station, Texas 77845

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

A study was conducted using 200 yearling Holstein steers. The cattle were fed supplemental feed for 92 days on coastal bermudagrass and bahiagrass pastures. There were 10 animals per pasture and 5 replications of each treatment. The results were as follows:

	Bambermycins (mg/head/day)			
	0.0	5.0	10.0	20.0
Average Daily Gain (kg)	0.465	0.469	0.505	0.602

Results of Efficacy Studies:

A randomized complete block design was used for all studies and the data were pooled by mixed model analysis of variance to determine the significance of the effect of bambermycins on average daily gain (ADG). A pooled analysis of the three (3) studies that tested bambermycins at 0, 10, 20, 40, 60 and 80 mg/head/day demonstrated that there was no improvement in average daily gain at dosages above 20 mg bambermycins/head/day which established the maximum effective dosage as 20 mg bambermycins/head/day. Therefore, because an improvement in average daily gain was not observed with the 40, 60 and 80 mg/head/day dosages of bambermycins, a pooled statistical analysis of the five (5) studies was conducted for treatments 0, 5, 10 and 20 mg bambermycins per head per day. Results of the pooled analysis demonstrated that bambermycins fed at 10 and 20 mg/head/day significantly increased ($P< .05$) the average daily gain (ADG) of steers and heifers consuming pasture when compared with the control steers and heifers. Steers and heifers responded similarly to the treatments. Approval of the dosage range of 10 to 20 mg bambermycins/head/day was based on the best fitting Andersen-Nelson linear plateau model. This was a linear model, on which 10 mg bambermycins/head/day was the first dose tested that was significantly better than controls. Results from the unweighted pooled analysis are presented in the following table.

POOLED ANALYSIS

	Bambermycins (mg/head/day)			
	0.0	5.0	10.0	20.0
Average Daily Gain (kg)	0.729	0.750	0.806	0.835

For Cattle Fed Free-Choice:

Summary of Efficacy Data (*As previously described in FOI Summary dated July 9, 1996 for GAINPRO® for Pasture Cattle Fed on a Free-Choice Basis: 61 FR 43654; August 26, 1996, approval.)*

Four (4) pivotal studies were conducted using a randomized complete block design and 512 growing calves. The studies are summarized and evaluated below for significant differences in rate of weight gain. The 512 test animals used in these four (4) pasture studies were fullbred or crossbred animals of European and exotic breeds. Each study contained replicates of non-medicated control and medicated animals for comparison purposes. Duration of the studies ranged from 98 to 101 days. Steers and heifers were used in all studies. Eight (8) steers or heifers were randomly assigned to each pasture. The initial animal weights ranged from 235 to 300 kg, and the studies were terminated when the animals reached 285 to 395 kg.

During the studies the cattle were rotated across pastures within a block to minimize any effect(s) of pasture conditions. The four (4) studies are summarized as follows:

Trial No. 946-01-02-94: Ruminant Free-Choice Type C Medicated Feed

Investigator: William C. Ellis
Colonial Farms
704 Encinas Place
College Station, Texas 77845

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

The study was conducted in Ruston, LA using 64 yearling steers and 64 yearling heifers. The cattle were fed bambermycins via loose mineral for 98 days on native coastal bermuda and bahia pastures. There were 8 animals per pasture and 8 replications of each treatment. The results were as follows:

Control	Bambermycins, as GAINPRO®, 120 g/ton

Average Daily Gain (kg/day)	0.399	0.479
Bambermycins (mg/head/day)	0.00	17.08

Trial No. 946-02-02-94: Ruminant Free-Choice Type C Medicated Feed

Investigator: Dr. Ed G. Johnson
Johnson Research
24007 Highway 20-26
Parma, ID 83660

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

The study was conducted in Parma, ID using 64 yearling steers and 64 yearling heifers. The cattle were fed bambermycins via loose mineral for 98 days on alta fescue and ladino clover pastures. There were 8 animals per pasture and 8 replications of each treatment. The results were as follows:

	Control	Bambermycins, as GAINPRO®, 120 g/ton
Average Daily Gain (kgs/day)	0.542	0.580
Bambermycins (mg/head/day)	0.00	5.01

Trial No. 946-03-02-94: Ruminant Free-Choice Type C Medicated Feed

Investigator: Dr. Daryl Meyer
Lucerne Enterprises
730 North Howard
Fremont, NE 68025

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

The study was conducted in Rose, NE using 64 yearling steers and 64 yearling heifers. The cattle were fed bambermycins via loose mineral for 98 days on native rye and sorghum pastures. There were 8 animals per pasture and 8 replications of each treatment. The results were as follows:

	Control	Bambermycins, as GAINPRO®, 120 g/ton
Average Daily Gain (kg/day)	0.807	0.852
Bambermycins (mg/head/day)	0.00	17.87

Trial No. 946-06-02-94: Ruminant Free-Choice Type C Medicated Feed

Investigator: Dr. Mary Wray
Horton Feedlot & Research Center
5100 East County Road 70
Wellington, CO 80549

Monitor: Lawrence E. Deetz
Intervet Inc.
405 State Street
Millsboro, Delaware 19966

This study was conducted in Laramie, WY using 64 yearling steers and 64 yearling heifers. The cattle were fed bambermycins via loose mineral for 101 days on native grass pasture consisting primarily of foxtail. There were 8 animals per pasture and 8 replications of each treatment. The results were as follows:

	Control	Bambermycins, as GAINPRO®, 120 g/ton	
Average Daily Gain (kg/day)	0.893	0.947	
Bambermycins (mg/head/day)		0.00	21.45

Results of Efficacy Studies:

A randomized complete block design was used for all studies and the data were pooled by analysis of variance to determine the significance of the effect of bambermycins on average daily gain (ADG). A pooled analysis of the four (4) studies that tested the free-choice Type C medicated feed demonstrated that there was a significant increase in the rate of weight gain with the bambermycins medicated feed when compared with the non-medicated feed.

Mixed model procedures were used to allow for the estimation of random and fixed effects and inference to the broad inference space. For average daily gain, the fixed effects included sex, treatment, and sex by treatment interaction. Random effects included site, site by treatment interaction, site by sex interaction, block within site by sex, and site by treatment by sex interaction. Treatment differences were determined using a one-sided test.

The consumption data reported as average daily consumption of bambermycins in mg per head per day from the medicated replications were evaluated weekly. These data were used to establish the average daily consumption of bambermycins for each study and for making an estimation of the variance in average bambermycins intake between the 7-day periods within the studies. The amount of variation in bambermycins intake was then described by calculating a Coefficient of Variation (C.V.).

Results of the pooled analysis demonstrated that bambermycins consumed at an average intake of 15.35 mg per head per day for the four studies significantly increased ($P < .016$) the average daily gain of cattle consuming pasture when compared with cattle not receiving bambermycins. Steers and heifers responded similarly to the treatments. Approval of the Type C feed was based on the significant increased average daily gain, an average daily consumption of bambermycins (for the combined analysis of the 4 studies) within the approved dose range of 10 and 20 mg/head/day, and an acceptable Coefficient of Variation for average daily drug intake of 51.19%. Results from the mixed model analysis are presented in the following table:

	POOLED ANALYSIS	
	Control	Bambermycins, as GAINPRO®, 120 g/ton
Average Daily Gain (kg/day)	0.660[a]	0.715[b]
Bambermycins (mg/head/day)	0.00	15.35

Average daily gain means with different superscripts differ $P < .016$, one-sided test.

3. TARGET ANIMAL SAFETY

The supplemental new animal drug application for GAINPRO references the target animal safety studies summarized in the FOI for NADA 141-034 (59 FR 15624, April 4, 1994). As described in that summary, bambermycins was fed at 0, 20, 100 and 300 mg/head/day for 160 days. No toxic effects were reported and the data indicate that bambermycins is safe at 7.5 times the highest approved dose of 40 mg/head/day in pasture cattle. The data from those studies demonstrate the safety of the new animal drug for the indications for use and dosage as given in Sections 1 and 2 above.

4. HUMAN SAFETY

Please see Freedom of Information summary dated March 4, 1994, for the use of bambermycins in pasture cattle (slaughter, stocker and feeder cattle): NADA 141-034 (59 FR 15624, April 4, 1994). As referenced in that summary, bambermycins was approved for use in pasture cattle without a withdrawal period, tolerance or regulatory method for tissue residues and no additional toxicology or residue testing was required for the pasture cattle approval. The dose tested in the referenced tissue residue study (400 mg/head/day) is 10 times the highest approved dose of 40 mg/head/day in pasture cattle.

Summaries of the human food safety studies conducted on bambermycins can be found in the Freedom of Information summary dated September 21, 1993, for confined cattle (58 FR 54286, 21 October 1993).

5. 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 of the implementing regulations. The data demonstrates that bambermycins when fed continuously in a free-choice or hand-fed supplemental feed to provide not less than 10 nor more than 40 mg/head/day when administered to pasture cattle (slaughter, stocker, feeder cattle, and dairy and beef replacement heifers) is safe and effective for the claim of increased rate of weight gain.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the layperson have been provided and the product will retain its over-the-counter marketing status.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

6. ATTACHMENTS

Facsimile labeling for each product are attached as indicated below:

1. GAINPRO® Type A Medicated Article (GAINPRO® 10)
2. Type B Blue Bird
3. Type C Medicated Feed (Blue Bird) for Hand-Fed Supplement
4. Type C Medicated Feed (Blue Bird) for Free-Choice Mineral Vitamin Supplement

Blue Bird Bambermycins

Supplemental Pasture Cattle Feed
Type B Medicated Feed
Must Be Mixed Before Feeding

INDICATIONS:
For increased rate of weight gain in pasture cattle (slaughter, stocker and feeder cattle, and dairy and beef replacement heifers).

ACTIVE DRUG INGREDIENT

Bambermycins	**100.0 – 800.0 g/ton**

GUARANTEED ANALYSIS

Crude Protein, not less than	__%
Crude Protein from non-protein nitrogen (NPN)[1], not more than	__%
Crude Fat, not less than	__%
Crude Fiber, not more than	__%
Calcium, not less than	__%
Calcium, not more than	__%
Phosphorous, not less than	__%
Salt[1], not less than	__%
Salt[1], not more than	__ %
Sodium[2], not less than	__ %
Sodium[2], not more than	__ %
Potassium, not less than	__ %
Vitamin A[1], not less than	__ IU/lb

[1] If added.
[2] Shall be guaranteed only when total Sodium exceeds that furnished by the maximum salt guarantee.

INGREDIENTS

Ingredients as defined by AAFCO.

MIXING DIRECTIONS

To manufacture Type C medicated feeds containing 2.0 to 80.0 g/ton bambermycins mix:

20 to 800 lb of Type B feed containing 100 g/ton bambermycins with 1980 to 1200 lbs of non-medicated feed, or
2.5 to 100 lb of Type B feed containing 800 g/ton bambermycins with 1997.5 to 1900 lbs of non-medicated feed.

Lot No.

NET WEIGHT ON BAG OR BULK

BLUE BIRD FEED MILLS
Any Town, USA 12345

Blue Bird Bambermycins

Cattle Hand-Fed Supplement
Type C Feed
MEDICATED

INDICATIONS:
For increased rate of weight gain in pasture cattle (slaughter, stocker and feeder cattle, and dairy and beef replacement heifers).

ACTIVE DRUG INGREDIENT

Bambermycins	**2.0 – 80.0 g/ton**

GUARANTEED ANALYSIS

Crude Protein, not less than	__%
Crude Protein from non-protein nitrogen (NPN)[1], not more than	__%
Crude Fat, not less than	__%
Crude Fiber, not more than	__%
Calcium, not less than	__%
Calcium, not more than	__%
Phosphorous, not less than	__%
Salt[1], not less than	__%
Salt[1], not more than	__ %
Sodium[2], not less than	__ %
Sodium[2], not more than	__ %
Potassium, not less than	__ %
Vitamin A[1], not less than	__ IU/lb

[1] If added.
[2] Shall be guaranteed only when total Sodium exceeds that furnished by the maximum salt guarantee.

INGREDIENTS

Ingredients as defined by AAFCO.

FEEDING DIRECTIONS

Feed continuously on a hand-fed basis at a rate of not less than 10 mg nor more than 40 mg of bambermycins per head per day. The drug must be contained in at least 1 lb. and not more than 10 lb. of supplemental Type C Medicated feed. Daily intakes of bambermycins in excess of 20 mg/head/day have not been shown to be more effective than 20 mg/head/day.

Lot No.

NET WEIGHT ON BAG OR BULK

BLUE BIRD FEED MILLS
Any Town, USA 12345

Blue Bird Bambermycins
Free-Choice Mineral and Vitamin Supplement
Type C Feed
MEDICATED

INDICATIONS:
For increased rate of weight gain in pasture cattle (slaughter, stocker and feeder cattle, and dairy and beef replacement heifers).

ACTIVE DRUG INGREDIENT

Bambermycins	**120 grams/ton**

GUARANTEED ANALYSIS

Calcium (CA), not less than	13.40%
Calcium (CA), not more than	16.00%
Phosphorous (P), not less than	7.90%
Salt (NaCl), not less than	18.00%
Salt (NaCl), not more than	21.60%

(Vitamins, minerals, dry matter, etc. may be guaranteed at discretion of manufacturer or requirements of AAFCO).

INGREDIENTS
Dicalcium phosphate, salt, calcium carbonate, processed grain by-products, magnesium oxide, mineral oil, yeast, iron oxide, magnesium sulfate, sodium selenite, copper sulfate, potassium sulfate, (plus listing of all vitamins and other trace minerals added to supplement).

FEEDING DIRECTIONS
Before feeding loose mineral containing bambermycins, be sure cattle are accustomed to mineral feeding and are not salt starved, by feeding non-medicated commercial mineral product for 6 weeks or until cattle have demonstrated consumption between 2.66 and 10.66 oz. per head per day.

As soon as cattle have demonstrated proper consumption, remove the non-medicated mineral and replace with the recommended amount of loose mineral containing bambermycins. Pasture and roughage should be adequate to assure consumption of the loose mineral supplement between 2.66 and 10.66 oz. per head per day (which provides 10 to 40 mg bambermycins per head per day). If cattle consume more or less than these levels, try moving the feeder further or closer to the general resting and watering area. Daily intakes of bambermycins in excess of 20 mg/head/day (5.33 oz. of supplement) have not been shown to be more effective than 20 mg/head/day.

Lot No.

NET WEIGHT ON BAG OR BULK

BLUE BIRD FEED MILLS
Any Town, USA 12345

*FDA Medicated Feed Mill Licence required for the manufacture of free-choice feeds. Must be manufactured to specification published in Code of Federal Regulations (61 FR 43654, August 26, 1996).