

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-340

B. Sponsor

Roussel-Uclaf
163, Avenue Gambetta
Paris, France

US Agent Name and Address (if applicable)

Hoechst-Roussel Agri-Vet Co.
Route 202-206 North
Somerville, NJ 08876

C. Proprietary Name

Lincomix[®], Stenorol[®]

D. Established Name

lincomycin, halofuginone hydrobromide

E. Dosage Form

Lincomycin and halofuginone hydrobromide are marketed as separate Type A medicated articles. The lincomycin Type A medicated article is sold in two concentrations: 4 and 20 grams lincomycin activity per pound. Halofuginone hydrobromide Type A medicated article is sold in one concentration: 2.72 grams of halofuginone hydrobromide activity per pound. The route of administration of these two drugs is oral via the feed. The recommended dosage is:

Lincomycin 2 - 4 g/ton

Lincomycin is added to finished broiler feed at concentrations ranging from 2 to 4 g/ton for improved feed efficiency.

Halofuginone hydrobromide

Halofuginone is added to finished broiler feed at a concentration of 2.72 g/ton for the prevention of coccidiosis caused by *E. tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. mivati* and *E. brunetti*.

The resultant feed containing the two drugs is then fed continuously as the sole ration. Feeds containing halofuginone hydrobromide must be withdrawn from broilers 4 days before slaughter

F. Indication

For the prevention of coccidiosis caused by *E. tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. mivati*, and *E. brunetti*; and for improved feed efficiency in broiler chickens.

G. Effect of Supplement

This supplement provides for <changes being approved> (Delete this section for Original approvals)

II. EFFECTIVENESS

A. Floor Pen Studies - Body Weight & Feed Efficiency:

The efficacy data for each individual drug is located in its parent NADA and that data is summarized in the parent FOI: halofuginone hydrobromide, NADA 130-951, approved August 21, 1985 (50 FR 33718); lincomycin, NADA 34-085, approved May 9, 1970, (35 FR 7300).

The New Animal Drug Application on which approval of lincomycin in combination with halofuginone hydrobromide is based contains adequate and well controlled studies demonstrating the effectiveness of lincomycin and halofuginone hydrobromide when feed to broilers. Four experiments using a randomized complete block design were conducted utilizing 13,096 broilers which were fed from one (1) day of age to market weight. These experiments are summarized and evaluated below for significant differences in feed efficiency.

In these four studies, pens were randomly assigned to treatments within blocks; 50 to 80 birds of equal sex were selected at random and assigned to each pen; 15 to 32 replications were used per treatment group.

The studies were done using only the combination of treatments necessary under a revised guideline for broiler combination efficacy studies (Guideline for Drug Combinations for Use in Animals, Center for Veterinary Medicine, October 1983). The Guideline provides for the granting of a range approval for production drugs in combination when the maximum level tested for the claim(s) is demonstrated to make a significant benefit to the combination. Thus, the following treatments from each of the five studies were pooled and subjected to statistical analysis:

Halofuginone hydrobromide - 2.72 g/ton

Lincomycin - 4 g/ton + Halofuginone hydrobromide - 2.72 g/ton.

Studies were designed to simulate varying conditions such as geographical location, differences in climate, changes in weather, differences in management practices, and degree of disease contamination of the premises. The chicks were grown on old litter and diets were balanced to provide adequate levels of all nutrients.

The effect of lincomycin on feed efficiency is presented in Table I.

Analysis of the combined data shows an overall significant ($p < 0.05$) increase in feed efficiency due to feeding lincomycin in the presence of halofuginone hydrobromide.

Therefore, under the Guideline, these data are adequate for the claims shown on Page 1, Item 2, under Indications for Use.

The floor pen studies for the feed efficiency claim were conducted by:

Dr. Carey Quarles
 Colorado Quality Research
 1401 Duff Drive
 Suite 700
 Fort Collins, CO 80524

Mr. Richard Roth
 Avian Services
 Frenchtown, NJ 08825

Dr. Larry McDougald
 Georgia Poultry Research
 PO Box 5822
 Athens, GA 30604

Mr. Perry Twining
 Research and Consulting Assoc. Inc.
 PO Box 1557
 Salisbury, MD 21801

Table 1 Feed Efficiency

Study Location	Pens per Treatment	Birds per Pen	Treatments* - Control	Treatments* - Lincomycin (4g/ton)
Colorado	32	50	1.969	1.940
New Jersey	24	80	1.948	1.928
Georgia	15	60	1.881	1.813
Maryland	24	74	1.909	1.920
Average			1.927	1.900

* All treatments contained halofuginone hydrobromide at 2.72/ton

B. Noninterference Battery Study

Fourteen day old broiler chickens were used in an adequate well controlled battery study to test for the noninterference of lincomycin on the anticoccidial efficacy of halofuginone hydrobromide. Recent field strain isolates of coccidia were used. Combinations of E. acervulina, E. maxima, E. tenella, E. brunetti, E. necatrix and E. mivati/mitis were used. This arrangement facilitated identification of lesions. The broilers were randomized and assigned to cages with 10 broilers per cage. There were four (4) replicates of each treatment group. Table 2 shows the treatments used in this battery study along with the results for average weight gain, dropping scores, lesion scores and coccidiosis mortality.

This battery study adequately demonstrates that there is no interference of lincomycin on the anticoccidial efficacy of halofuginone hydrobromide. Therefore, this combination is compatible.

The investigator involved in the above battery study was:

Dr. Carey Quarles
 Colorado Quality Research
 1401 Duff Drive; Suite 700
 Fort Collins, CO 80524

III. TARGET ANIMAL SAFETY

The original NADA's contain FOI summaries and complete information on the safety to the target animal of the two products (NADA 34-085, lincomycin published May 9, 1970, [35 FR 7300] NADA 130-951, halofuginone hydrobromide published August 21, 1985, [50 FR 33178]). The effectiveness studies, described in Section 4 above, adequately demonstrated that there were no toxicological or pharmacological effects when the two drugs were combined indicating that they are compatible in combination when used in poultry.

Table 2 Average Weight Gain, Dropping Score, Coccidiosis Mortality and Total Lesion Scores for the Noninterference Battery Study *

Treatment**	Av Gain (g)	Tot. Drop Sc	Tot. Les. Sc	%Cocc. Mort.
NM	172/170	1/1	0.0/0.0	0.0/0.0
NM 1	94/52	2.8/2.8	6.3/8.0	35.0/42.5
Halo.	162/171	1.6/1.5	2.6/3.1	7.5/0.0
Lin.	95/81	2.7/2.9	5.4/7.4	35.0/45.0
Halo. +Lin.	162/170	1.6/1.5	2.6/2.5	2.5/2.5

*Infection I - E. maxima, E. acervulina, E. tenella
 Infection II - E. mivati/mitis, E. necatrix, E. brunette

** NM = non medicated, uninfected
 NM 1 = non medicated, infected
 Halo = halofuginone at 2.72 g/ton
 Lin = Lincomycin at 4 g/ton

The summary of the safety data in the parent NADA's combined with the summary of the efficacy floor pen trials and non interference battery study for the combination product demonstrate normal growth with no incidence of disease or other abnormality.

A Safety Growth Study

Investigator:

Drs. P. Griminger & H. Fisher
 Dept. of Nutrition
 Cook College/Rutgers University
 New Brunswick, NJ 08903

The following table shows that the broilers grew well and feed efficiency was not adversely affected by any of the treatments.

Table 3 Safety Study Summary - Seven Week Data

Treatment	Drug Level	Broiler Number	Final Body Wt. (lbs)	Final Feed Efficiency
Control		150	3.52	2.74
Halofuginone hydrobromide	2.72 g/ton	100	3.89	2.50
Lincomycin	4 g/ton	100	3.89	2.50
Roxarsone	0.005%	100	3.89	2.50

The data provided corroborative evidence of the Safety and Efficacy of the combination of halofuginone hydrobromide and lincomycin in the feed of broiler chickens and these data are consistent with and fulfill all the requirements for a fixed combination drug for animals as follows:

- a. Each drug component makes a contribution to the claimed effects.
- b. The dosages of each drug component are such that the combination is safe and effective.
- c. This combination demonstrates significant control of a specific disease condition for a large patient animal population. Specifically, *Eimeria tenella* is a major widespread organism of coccidiosis and the most pathogenic *Eimeria* species and, as such, possesses the potential of causing extensive economic losses to broiler producers. The label claims are not antagonistic.
- d. Based on the data in the parent NADA's, the compatibility battery studies and the floor pen efficacy studies, we concluded that the combination of these two drugs is safe to feed to broiler chickens as indicated by the label.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests:

The original NADA's contain FOI summaries and complete information of human food safety on the two products (NADA 34-085, lincomycin published May 9, 1970, [35 FR 7300] NADA 130-951, halofuginone hydrobromide published August 21, 1985, [50 FR 33178]).

B. Safe Concentration or Tolerance of Residues:

Halofuginone hydrobromide has an established tolerance in broiler chickens of 0.1 ppm for parent halofuginone hydrobromide (marker residue) in liver which is the target tissue (21 CFR 556.308). A marker residue concentration of 0.1 ppm in liver corresponds to a concentration for total residues of halofuginone hydrobromide of 0.3 ppm in the liver, (21 CFR 556.308). The safe concentrations for total halofuginone hydrobromide in the uncooked edible tissues of broiler chickens are 0.1 ppm in muscle, 0.3 ppm in liver and 0.2 ppm in skin with adhering fat, (21 CFR 556.308).

The tolerances for lincomycin are established at 0.1 ppm for negligible residues in the edible tissues of broiler chickens, (21 CFR 556.360).

C. Residue Depletion Noninterference Study

The residue data supporting the approved individual uses of halofuginone hydrobromide and lincomycin and their respective withdrawal times of four and zero days have been submitted in their respective original applications. The summary of the study conducted for this combination is presented in Table IV and establishes that each drug in the presence of the other does not exceed its established safe concentration(s) or tolerance(s) and that none of the drugs interferes with the other's tissue residue assay. The broilers in that study were fed the combination of halofuginone hydrobromide (2.72 g/ton), lincomycin (4 gm/ton) and roxarsone (45.4 g/ton) for 49 days prior to the withdrawal period. Edible tissues, including liver, muscle and skin/fat were assayed for drug residues. The edible tissues were collected on the withdrawal dates indicated in Table VI.

Investigator for the tissue residue study:

Dr. Carey Quarles
 Colorado Quality Research Inc.
 1401 Duff Drive
 Suite 700
 Fort Collins, CO 80524

Table 4 Residue Depletion Study Assay Results (ppm)

Drug	Withdrawal Day Assay	Tissue*-Liver	Tissue*-Skin/Fat	Tissue*-Muscle
Lincomycin	0	ND**	ND	ND
Halofuginone hydrobromide	2	0.06 (0.02)		
Halofuginone hydrobromide	3	0.04 (0.01)		
Halofuginone hydrobromide	4	0.02 (0.01)		
Halofuginone hydrobromide	5	0.01 (0.007)		

* Average of 6 birds except for halofuginone hydrobromide at day 5 withdrawal the average is from five birds; standard deviation in parentheses.

** ND = None detected; sensitivity of method is 0.1 ppm.

D. Assay Noninterference:

Along with the residue depletion results presented in Table IV, the sponsor conducted a noninterference study for the lincomycin tissue assay by spiking samples with lincomycin (0.15 ppm) and halofuginone hydrobromide (0.30 ppm) and conducting assays for lincomycin residues. The results demonstrated no interference by halofuginone hydrobromide on the assay for lincomycin.

The sponsor conducted a noninterference study for halofuginone hydrobromide by spiking control tissue samples with halofuginone hydrobromide (0.10 ppm) and lincomycin (0.20 ppm) and then assaying these tissues for halofuginone hydrobromide content. The results demonstrated no interference by lincomycin on the tissue assay for halofuginone hydrobromide.

A 4 day withdrawal period is established for this combination based on a 99% statistical tolerance limit with 95% confidence. These data support a 4 day withdrawal for the halofuginone hydrobromide/lincomycin combination.

E. Regulatory Methods

The tissue assay method for halofuginone hydrobromide is an HPLC method titled, "Analysis of an Anti-coccidial Drug, Halofuginone , in Poultry Tissue". The method is on file at the Center for Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

The tissue assay method for lincomycin is a microbiological method titled "Standard Operating Procedure for a Tissue Residue Study in Broiler Chickens Treated with Lincomycin, U-10, 149A". The method is on file at the Center for Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Act and demonstrate that halofuginone hydrobromide (2.72 g/ton) plus lincomycin (2 to 4 g/ton) are safe and effective when fed to broiler chickens at the dosage levels for the indications stated in Section 3 of this FOI Summary.

Under the Center's supplemental policy (42 FR 64367; December 23, 1977) this original application is regarded as a Category 2 supplemental NADA which did not require a reevaluation of safety and efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with the labeling as approved in the parent NADAs.

Residue depletion studies in this application demonstrate the halofuginone hydrobromide depletes to safe concentration within four (4) days withdrawal to no more than 0.1 ppm in muscle, 0.3 ppm in liver and 0.2 ppm in skin/fat (21 CFR 556.308); lincomycin is below the tolerance of 0.1 ppm at zero withdrawal (21 CFR 556.360). Adequate information was submitted to demonstrate noninterference between the assays for each drug. The approval of this application will not significantly increase exposure of humans to residues of the drugs.

The data from six well controlled trials demonstrate the effectiveness of lincomycin for improved feed efficiency in the presence of halofuginone hydrobromide when mixed in broiler chicken feeds. The data from noninterference battery study demonstrated the effectiveness of halofuginone hydrobromide in preventing coccidiosis in the presence of lincomycin. CVM's guideline for drug combinations for use in animals provides for the granting of range approval for lincomycin as shown in Section 3 of this document. A four (4) day withdrawal period is required before the broiler chickens may be slaughtered for human food.

VI. ATTACHMENTS

1. Bag label.

Copies of this label may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.