Date of Approval: May 22, 2009

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-293

AVATEC plus 3-NITRO

Lasalocid sodium plus Roxarsone
Type A medicated articles to be used in the manufacture of Type C medicated feeds
Growing Turkeys

For the prevention of coccidiosis caused by *Eimeria meleagrimitis, E. gallopavonis,* and *E. adenoeides,* for increased rate of weight gain, improved feed efficiency and improved pigmentation in growing turkeys.

Sponsored by:

Alpharma Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-293
B. Sponsor:	Alpharma Inc. 440 Rte. 22 Bridgewater, NJ 08807 Drug Labeler Code: 046573
C. Proprietary Names:	AVATEC plus 3-NITRO
D. Established Names:	Lasalocid sodium Roxarsone
E. Pharmacological Categories:	Anticoccidial and arsenical
F. Dosage Form:	Type A medicated article to be used in the manufacture of Type C medicated feeds
G. Amount of Active Ingredients:	Lasalocid sodium – 90.7 g/lb (20 %) Roxarsone – 90.7 g/lb (20%)
H. How Supplied:	Lasalocid sodium – 50 lb bag Roxarsone – 50 lb bag
I. How Dispensed:	OTC
J. Dosage:	Lasalocid sodium - 68 to 113 g/ton Roxarsone - 22.7 to 45.4 g/ton
K. Route of Administration:	Oral, in feed
L. Species/Class:	Growing turkeys
M. Indications:	For the prevention of coccidiosis caused by *Eimeria meleagrimitis*, *E. gallopavonis*, and *E. adenoeides*, for increased rate of weight gain, improved feed efficiency and improved pigmentation in growing turkeys.

II. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act (ADAA) of 1996, if the animal drugs or active ingredients intended for use in combination in an animal feed have already been separately approved for the particular uses and conditions for which they are intended for use in combination, the Center for Veterinary Medicine (CVM) will not refuse to approve an NADA for the combination on effectiveness grounds unless the FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness
- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Lasalocid sodium, as provided by Alpharma Inc., has previously been separately approved for use in feed for growing turkeys for the prevention of coccidiosis caused by *Eimeria meleagrimitis*, *E. gallopavonis*, and *E. adenoeides* (21 CFR 558.311). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in feed for growing turkeys for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530). Effectiveness of each drug, lasalocid sodium and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADAs 096-298 and 007-891 for lasalocid sodium and roxarsone, respectively.

Because lasalocid sodium and roxarsone each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that lasalocid sodium plus roxarsone provide appropriate concurrent use for the intended target population. The use of lasalocid sodium plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (lasalocid sodium - coccidiosis, and roxarsone - increased rate of weight, improved feed efficiency, and improved pigmentation) likely to occur simultaneously with sufficient frequency in growing turkeys. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed.

III. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on target animal safety grounds unless:

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and CVM finds that the application fails to show that the combination is safe, or
- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and CVM finds that the application fails to show that the combination is safe.

Lasalocid sodium, as provided by Alpharma Inc., has previously been separately approved for use in feed for growing turkeys for the prevention of coccidiosis caused by *Eimeria meleagrimitis*, *E. gallopavonis*, and *E. adenoeides* (21 CFR 558.311). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in feed for growing turkeys for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530).

Under the provisions of ADAA, this original approval allows for the combination of lasalocid sodium (as provided by Alpharma Inc.) and roxarsone (as provided by Alpharma Inc). Target animal safety for each drug, lasalocid sodium and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADAs 096-298 and 007-891 for lasalocid sodium and roxarsone, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of lasalocid sodium and roxarsone when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Therefore, in accordance with the FFDCA, as amended by the ADAA of 1996, no specific target animal safety studies are required for approval of this application.

IV. HUMAN FOOD SAFETY:

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or

- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Toxicology:

Safety of the individual drugs in this combination product has been established by data in NADA 096-298 for lasalocid sodium (approved October 8, 1976, 40 FR 44382), NADA 007-891 for roxarsone (approved March 23, 1951).

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Residue Depletion Study

Tissue Residue Study for the Combination of Lasalocid, Bacitracin Methylene Disalicylate and Roxarsone in Turkeys.

Study Project No. RT-004-07LAMBRO

Study Director- Stephen W. Davis, DVM, Dip. ACPV
Colorado Quality Research, Inc., Wellington, CO

Testing Facility- Colorado Quality Research, Inc., Wellington, CO

Thirty-two (32) turkeys (*Meleagris gallopavo*; 16 males, 16 females) approximately 10 weeks of age were fed 113 g lasalocid sodium/ton, 45.4 g roxarsone/ton, and 200 g BMD/ton for four weeks. Six hours after removal of medicated feed (practical zero withdrawal), eight birds (4M, 4F) were sacrificed to examine lasalocid residues in liver. For liver arsenic (roxarsone) residues, four groups of birds (3M, 3F) were sacrificed at 0, 1, 3, and 5 days withdrawal. Control birds fed a basal diet were sacrificed at week three. Livers were collected and samples stored at -20ºC until analyzed.

Liver arsenic residue levels were analyzed using the sponsor's method SAP 010-550.2, "Total Arsenic Residues in Animal Tissues", which is a direct reference to AOAC method 973.78, "Arsenic (Total) Residues in Animal Tissues- Spectroscopic Method." Lasalocid residues in liver were analyzed using the regulatory method "HPLC Assay of Turkey Liver for Intact Lasalocid (Ro 2-2985)", with minor modifications. Mean arsenic residues in liver for each withdrawal period are summarized in Table 1.

Table 1. Summary of Total Arsenic Concentrations (in ppm) Measured in Tissues of Turkeys Medicated with BMD (200 g/ton), Lasalocid (113 g/ton) and Roxarsone (45.4 g/ton)

Withdrawal Period (days)	Total Arsenic (ppm) in Liver
0	1.855

1	0.586
3	0.573
5	0.180

At 5 days after the last dose, the prescribed withdrawal period for the combination, total arsenic residues in the livers of treated birds were below the tolerance given in 21 CFR 556.60.

The requirement for assay noninterference data for bacitracin MD has been waived. Data to show that bacitracin does not interfere with the method for arsenic are not necessary because the analysis for arsenic involves ashing.

Even though a withdrawal period is not required for lasalocid residues in turkey if residues are below the tolerance of 0.4 ppm at practical zero withdrawal, the combination would have a withdrawal period of at least five days. Nevertheless, we conducted a statistical analysis of the lasalocid data to determine the 99^{th} percent tolerance limit with 95% confidence to confirm residues are below the tolerance. We used the following equation:

99^{th} percent tolerance limit with 95% confidence = Mean + (S.D.)(k value)

We found that at practical zero withdrawal:

99^{th} percent tolerance limit with 95% confidence= 0.02725+ (0.00783)(4.355) = 0.061 ppm

The calculation fell below the tolerance of 0.4 ppm for lasalocid in turkey liver.

Thus, the results of the study demonstrate that residues of both drugs will be well below their respective tolerances at 5 days withdrawal.

2. Target Tissue and Marker Residue Assignment

The target tissue for parent lasalocid (the marker residue for lasalocid sodium) in turkeys is liver (21 CFR 556.347). A target tissue for arsenic residues from roxarsone has not been assigned.

3. Tolerance Assignments

The tolerance for parent lasalocid (the marker residue) in liver (the target tissue) is 0.4 ppm. The tolerance for parent lasalocid (the marker residue) in skin with adhering fat is 0.4 ppm (21 CFR 556.347). The tolerances for total residues of combined arsenic from roxarsone in turkeys are established at 0.5 ppm in uncooked muscle tissue and eggs and 2 ppm in uncooked edible by-products (21 CFR 556.60).

4. Withdrawal Time

The results of the study summarized in 1a. demonstrate that residues of both drugs will be well below their respective tolerances at 5 days withdrawal. A withdrawal period of 5 days is assigned for the combined use of lasalocid up to 113 g/ton plus roxarsone up to 45.4 g/ton.

C. Microbial Food Safety:

The Agency determined that an assessment of microbial food safety associated with this combination of lasalocid and roxarsone in Type C Medicated turkey feeds, approvable pursuant to the provisions of the Animal Drug Availability Act (1996), was not necessary at this time.

D. Analytical Method for Residues:

1. Determinative and Confirmatory Methods

The original approval of NADA 096-298 for lasalocid sodium dated October 8, 1976 (40 FR 44382), and NADA 007-891 for roxarsone dated March 23, 1951, contain the analytical method summaries for lasalocid and arsenic in turkeys.

2. Availability of Method

The validated regulatory methods for detection and confirmation of residues of lasalocid and arsenic are available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The product labeling does not contain any information on the Type C medicated feed labeling regarding safety to humans handling, administering, or exposed to the Type C medicated feed.

VI. 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. The data contained in the previously approved NADAs for AVATEC plus 3-NITRO demonstrate that, when they are used according to the label, they are safe and effective for the prevention of coccidiosis caused by *Eimeria meleagrimitis*, *E. gallopavonis*, and *E. adenoeides*, for increased rate of weight gain, improved feed efficiency, and improved pigmentation in growing turkeys. Additionally, data demonstrate that residues in food products derived from growing turkeys treated with AVATEC plus 3-NITRO will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity:

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

C. Patent Information:

No patents were submitted with this application.

VII. ATTACHMENTS:

Final Printed Labeling:
Lasalocid and Roxarsone Growing Turkey Ration Type C Medicated Feed