## I. GENERAL INFORMATION

### A. File Number

NADA 140-954

### B. Sponsor

Hoechst-Roussel Agri-Vet Company
Route 202-206 North
Somervile, New Jersey 08876-1258

### C. Proprietary Name

Lincomix®, Type "A" Medicated Article (Premix)

### D. Established Name

fenbendazole, lincomycin

### E. Dosage Form

Fenbendazole and lincomycin are marketed as separate Type "A" medicated articles. The fenbendazole Type A medicated article is sold in three concentrations: 40, 80, or 200 grams of fenbendazole activity per kilogram. Lincomycin Type "A" medicated article is sold in two concentrations: 20 and 50 grams of lincomycin per pound.

### F. Dosage Regimen

**Fenbendazole-10 to 80 g/ton:** To provide a total dose of 9 mg/kg of body weight; the total dose is divided over a period of 3 to 12 days.
**Lincomycin:**
**20 g/ton:** For increased rate of gain in growing-finishing swine.
**40 g/ton:** For control of swine dysentery. For use in swine on premises with a history of swine dysentery, but where symptoms have not yet occurred.
**100 g/ton:** For treatment of swine dysentery.
**200 g/ton:** For reduction in the severity of swine mycoplasmal pneumonia caused by *Mycoplasma hyopneumoniae.*
Notes: The resultant feed containing both drugs is then fed as the sole ration. Feed containing lincomycin at 100 or 200 g/ton must be withdrawn 6 days prior to slaughter.

### G. Route of Administration

oral via the feed

### H. Species/Class

Swine

### I. Indication

Fenbendazole is indicated for the removal of:

**Lungworms:**

*Metastrongylus apri, Metastrongylus pudendotectus* .

Check verbatim label for Type 'A" products.

**Gastrointestinal worms:**

large roundworms (*Ascaris suum*) adult and larvae (L3 & L4 stages; liver, lung and intestinal forms), nodular worms (*Oesophagostomum dentatum, O. quadrispinulatum* ), small stomach worms (*Hyostrongylus rubidus* ) adult and larvae (L2, L3, L4 stages; intestinal mucosal forms), and whipworms (*Trichuris suis*)

**Kidneyworms:** *Stephanurus dentatus*, adult and larvae

**Lincomycin is indicated for:**

- increased rate of weight gain in growing-finishing swine
- for control of swine dysentery; for use in swine on premises with a history of swine dysentery, but where symptoms have not yet occurred
- for treatment swine dysentery
- for reduction in the severity of swine mycoplasmal pneumonia caused by *Mycoplasma hyopneumoniae*.

## II. EFFECTIVENESS

The efficacy data for each individual drug are located in its parent NADA. The Freedom of Information (FOI) Summary contains a summary.

| | | | |
|---|---|---|---|
| Fenbendazole | NADA 131-675 | 49 FR 3845<br>55 FR 48230 | Jan. 31, 1984<br>Nov. 20, 1990 |
| Lincomycin | NADA 97-505 | 41 FR 26855<br>47 FR 52145<br>51 FR 12137<br>55 FR 23423 | Jun. 30, 1976<br>Nov. 19, 1982<br>Apr. 9, 1986<br>Jun. 8,1990 |

Lincomycin is a continuous use production drug (fed longer than 14 days) and fenbendazole is a short term therapeutic treatment. The study required for this type of approval is one that demonstrates the effectiveness of fenbendazole when fed in combination with lincomycin (see Center for Veterinary Medicine *Staff Manual Guide* , IV. Supplemental Policies, Guide 1240.4145, dated 4/16/90). A controlled critical experiment was conducted using 80 pigs which were experimentally infected. The experiment demonstrated significant differences in parasite removal and is summarized below.

Eighty pigs were experimentally infected with *Ascaris suum* and *Trichuris suis* . The pigs were randomly assigned to 8 treatment groups of 10 each; each treatment group contained 2 replicates of 5 each. The analysis of the data shows a significant reduction ($p < .05$) in the number of parasites present in animals receiving fenbendazole. The treatment groups and data are summarized in Table 1.

This study was conducted by T.S. van Veen, Veterinary Clinical Center, Michigan State University, East Lansing, Michigan 48824.

**Table 1. Mean Number of *Ascaris suum and Trichuris suis*.**

| **Treatment Group** | ***Ascaris suum*** | ***Trichuris suis*** |
|---|---|---|
| Control | 9.3 (18.4) | 133.9 (90.36)a |
| FBZ 3 mg/kg x 3 days | 0.0 (0.0)b | 6.3 (6.98)b |
| FBZ 1.5 mg/kg x 6 days | 0.0 (0.0)b | 0.5 (1.58)c |
| FBZ 75 mg/kg x 12 days | 0.0 (0.0)b | 99.8 (85.57)a |
| FBZ 3 mg/kg x 3 days<br>LI 200 g/ton | 0.0 (0.0)b | 1.6 (2.01)b,c |
| FBZ 1.5 mg/kg x 6 days<br>LI 200 g/ton | 0.0 (0.0)b | 6.2 (19.26)b,c |
| FBZ 75 mg/kg x 12 days<br>LI 200 g/ton | 0.0 (0.0)b | 2.1 (3.45)b |
| LI 200 g/ton | 4.0 (7.96)a | 88.7 (65.42)a |

Note:

FBZ = fenbendazole, LI = lincomycin.
Numbers in parentheses are standard deviation.
Means within columns with different superscripts are different $p < 0.5$.

From these data it can be concluded that the efficacy of fenbendazole against *A. suum* and *T. suis* is not altered by the concurrent use of lincomycin.

## III. TARGET ANIMAL SAFETY

The target animal safety data for each individual drug are located in its parent NADA. The FOI contains a summary of the data.

| | | | |
|---|---|---|---|
| Fenbendazole | NADA 131-675 | 49 FR 3845<br>55 FR 48230 | Jan. 31, 1984<br>Nov. 20, 1990 |
| Lincomycin | NADA 97-505 | 41 FR 26855<br>47 FR 52145<br>51 FR 12137<br>55 FR 23423 | Jun. 30, 1976<br>Nov. 19, 1982<br>Apr. 9, 1986<br>Jun. 8,1990 |

The New Animal Drug Application upon which approval of fenbendazole in combination with lincomycin is based contains an adequate and well-controlled study demonstrating the safety of the combination when administered in the feed to pigs. This study was designed to evaluate the target animal safety aspects of animals treated with various dosages of fenbendazole and lincomycin. Forty pigs weighing approximately 35 lbs were divided into 4 groups of 10 pigs each. Treatment regimens reflected 0, IX, 3X or 5X the suggested maximum dosage treatments (fenbendazole = 3 mg/kg for 3 days, 9 mg/kg for 9 days, or 15 mg/kg for 9 days, lincomycin = 200 g/t, 600 g/t or 1000 g/t for 21 days).
This study was conducted by T. S. van Veen, Veterinary Clinical Center, Michigan State University, East Lansing, Michigan 48824.
Parameters measured included body weight (weekly), clinical observations (daily), clinical chemistry and hematology (onset, middle, and termination of study). The

latter two parameters included complete blood count, activated partial thromboplastin time, serum chemistry profile, and serum electrolyte profile. None of the parameters measured at any dosage were outside of physiological ranges.
This study demonstrates normal physiological function (used as a measure of safety) when fenbendazole and lincomycin are administered concomitantly in feed to pigs.

## IV. HUMAN FOOD SAFETY

### A. Toxicity Tests

The original NADA's and FOI summaries for each drug demonstrate that food from animals fed these products is safe for human consumption.

| | | | |
|---|---|---|---|
| Fenbendazole | NADA 131-675 | 49 FR 3845<br>55 FR 48230 | Jan. 31, 1984<br>Nov. 20, 1990 |
| Lincomycin | NADA 97-505 | 41 FR 26855<br>47 FR 52145<br>51 FR 12137<br>55 FR 23423 | Jun. 30, 1976<br>Nov. 19, 1982<br>Apr. 9, 1986<br>Jun. 8,1990 |

### B. Safe Concentration of Residues

In swine a tolerance of 0.1 ppm lincomycin is established for negligible residues in the edible tissues (21 CFR 556.360). A tolerance for marker residues of fenbendazole in swine is not needed. The safe concentration for total residues of fenbendazole in uncooked edible tissues of swine are 5 ppm in muscle, 15 ppm in liver, 20 ppm in kidney, and 20 ppm in skin and fat (21 CFR 556.275).

### C. Residue Depletion Non-interference Study

The residue data supporting the approved individual uses of fenbendazole and lincomycin have been submitted in their respective original applications. The summaries of the study conducted for this combination are presented in Tables 2, 3 and 4. These summaries establish that each drug in the presence of the tolerance(s) and that none of the drugs interferes with the other's tissue residue assay. The pigs in this study were fed lincomycin (100 g/t or 200 g/t) for 12 days prior to the withdrawal period in combination with fenbendazole (total dose of 9 mg/kg divided over 3 or 12 days) for 3 or 12 days prior to the withdrawal period. Liver and kidney were collected and assayed for lincomycin residues. Liver was also assayed for fenbendazole residues (fenbendazole assay detection limit 0.02 ppm, lincomycin assay detection limit 0.067 ppm). The tissues were collected on the withdrawal days indicated in Tables 2, 3 and 4.

Studies conducted by T.S. van Veen, MSU, East Lansing, Michigan 48824.

**Table 2. Residue Depletion Assay Results of Fenbendazole (ppm); Average values (n = 4); Standard Deviation in parentheses.**

| Treatment | Tissue | Withdrawal (hr) | Concentration (ppm) |
|---|---|---|---|
| FBZ 3 days; LI 200 g/ton | Liver | 12 | .116 (0.7) |
| FBZ 12 days; LI 200 g/ton | Liver | 12 | .049 (.07) |
| FBZ 3 days; LI 100 g/ton | Liver | 12 | .992 (.90) |
| FBZ 12 days; LI 100 g/ton | Liver | 12 | .113 (.04) |

**Table 3. Residue Depletion Assay Results of Lincomycin (ppm); Average values (n = 4); Standard Deviation in parentheses.**

| Treatment | Tissue | Withdrawal (hr) | Concentration (ppm) |
|---|---|---|---|
| FBZ 3 days; LI 200 g/ton | Liver | 12 | .02 (.04) |
| | Liver | 24 | .00 (.00) |
| | Liver | 72 | .06 (.07) |
| | Liver | 144 | .00 (.00) |
| FBZ 12 days; LI 200 g/ton | Liver | 12 | .06 (.04) |
| | Liver | 24 | .02 (.03) |
| | Liver | 72 | .15 (.20) |
| | Liver | 144 | .00 (.00) |
| FBZ 3 days; LI 100 g/ton | Liver | 12 | .02 (.03) |
| | Liver | 24 | .00 (.00) |
| | Liver | 72 | .04 (.06) |
| | Liver | 144 | .00 (.00) |
| FBZ 12 days; LI 100 g/ton | Liver | 12 | .00 (.00) |
| | Liver | 24 | .00 (.00) |
| | Liver | 72 | .00 (.00) |
| | Liver | 144 | .00 (.00) |

**Table 4. Residue Depletion Assay Results of Lincomycin (ppm) in Kidney: Average values (n=4); Standard Deviation in parentheses.**

| Treatment | Tissue | Withdrawal (hr) | Concentration (ppm) |
|---|---|---|---|
| FBZ 3 days; LI 200 g/ton | Kidney | 12 | .15 (.10) |
| | Kidney | 24 | .06 (.04) |
| | Kidney | 72 | .11 (.11) |
| | Kidney | 144 | .00 (.00) |
| FBZ 12 days; LI 200 g/ton | Kidney | 12 | .09 (.06) |
| | Kidney | 24 | .08 (.01) |
| | Kidney | 72 | .27 (.22) |
| | Kidney | 144 | .00 (.00) |
| FBZ 3 days; LI 100 g/ton | Kidney | 12 | .10 (.03) |
| | Kidney | 24 | .00 (.00) |
| | Kidney | 72 | .11 (.10) |
| | Kidney | 144 | .00 (.00) |
| FBZ 12 days; LI 100 g/ton | Kidney | 12 | .08 (.01) |
| | Kidney | 24 | .01 (.02) |
| | Kidney | 72 | .09 (.06) |
| | Kidney | 144 | .03 (.05) |

Along with the residue depletion results presented in Tables 2, 3 and 4, the sponsor conducted a noninterference study for the fenbendazole tissue residue study by spiking samples with fenbendazole and lincomycin and conducting fenbendazole assays. The results demonstrated no interference by lincomycin on the assay for fenbendazole. The sponsor conducted a noninterference study for lincomycin by spiking control tissue samples with lincomycin and fenbendazole and then assaying these tissues for lincomycin content. The results demonstrated no interference by fenbendazole on the tissue assay for lincomycin.

**D. Withdrawal Time:**

The data support a zero withdrawal for fenbendazole in swine tissues. Feeds medicated with 100 or 200 g/t lincomycin must be withdrawn 6 days before swine are slaughtered.

**E. Category Type**

Under 21 CFR 558.3 (b)(1)(ii), fenbendazole is classified as a Category II drug because a withdrawal period is required for the lowest use level in cattle feed. A withdrawal period is also required for the use of lincomycin at 100-200 g/ton levels in swine. Therefore, Medicated Feed Applications (FD 1900's) will be required for the combination of fenbendazole and lincomycin in swine feeds.

Under Section 21 CFR 558.4 (e) when drugs from both categories are used in combination, [Lincomycin (Category I) & Fenbendazole (Category II)] the Category II requirements will apply to the combination.

### F. Regulatory Methods

A microbiological assay method is used to assay tissues for lincomycin residues. The method titled "Determination of Lincomycin Residues in Broiler Chicken Tissues" is on file at the Center for Veterinary Medicine, Food and Drug Administration (HFV-199) 7500 Standish Place, Rockville, MD 20855.

An HPLC assay method is used to assay tissues for fenbendazole. This method titled "Determinative Procedure for the Measurement of Fenbendazole in Bovine Liver Tissue" is on file at the Center for Veterinary Medicine, Food and Drug Administration (HFV-199) 7500 Standish Place, Rockville, MD 20855.

## V. AGENCY CONCLUSIONS

The data submitted in support of this NADA, satisfy the requirements of Section 512 of the Act and demonstrate that the combination of fenbendazole and lincomycin, when fed to growing swine under its labeled conditions of use, is safe and effective.

Because this drug contains a combination of two previously approved active ingredients, this original new animal drug application is treated as a Category II drug [21 CRF 514.106 (b) (2)]. A reevaluation of underlying safety and effectiveness data in the two parent applications was not required.

The sponsor demonstrated via residue depletion studies using approved regulatory methods, that the depletion characteristics of the marker residue for each drug in the combination were not significantly modified. Based on the lack of significant change in depletion characteristics, CVM concluded that the composition of the residue for each drug is not changed. The sponsor also demonstrated that the existing regulatory method for each drug is not interfered with by residues of the other drug. Based on the foregoing, it was not necessary to reevaluate the underlying toxicity tests supporting the separate approvals, or to require additional metabolism and total residue depletion studies.

Adequate directions for use of this combination product by nonveterinarians have been clearly written, and there is reasonable certainty that the conditions of use, including mixing directions, as stated on the label can and will be followed by the feed mill and producer. Approved over-the-counter products containing fenbendazole and lincomycin alone are marketed for the same claims as are on the label for the combination product. The Agency is not aware of any reason why the combining of the two products would require restriction of the new product to prescription use.

Under Section 512(c)(2)(F)(ii) of the Act, this approval qualifies for a three-year period of exclusivity to NADA's for the previously approved active ingredients because new clinical trials, field investigations, and human food safety data were required for approval.

## VI. LABELING (Attached)

Copies of applicable labels 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.