Approval Date: January 29, 1993

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-916

B. Sponsor

Fermenta Animal Health Company
10150 N. Executive Hills Boulevard
Kansas City, Missouri 64153

C. Proprietary Name

DENAGARD® Liquid Concentrate

D. Established Name

tiamulin

E. Dosage Form

liquid concentrate (12.3% tiamulin hydrogen fumarate)

F. Route of Administration

oral, via drinking water

G. Recommended Dosages:

For swine dysentery
3.5 mg tiamulin per pound body weight daily for 5 consecutive days

For swine pneumonia
10.5 mg tiamulin per pound body weight daily for 5 consecutive days

H. Indication

For the treatment of swine dysentery associated with *Treponema hyodysenteriae* and swine pneumonia due to *Actinobacillus pleuropneumoniae* susceptible to tiamulin.

II. EFFECTIVENESS

The effectiveness of DENAGARD® (tiamulin) in the treatment of swine dysentery associated with *Treponema hyodysenteriae* is discussed in detail in the FOI Summary of original NADA 134-644 (DENAGARD® Soluble Antibiotic). The effectiveness of tiamulin in the treatment of swine pneumonia due to *Actinobacillus pleuropneumoniae* is detailed in the FOI Summary for the supplement to NADA 134-644 for that use (48 FR 41384, September 15, 1983).

A crossover bioequivalence study using 20 crossbred pigs (10 barrows and 10 gilts) averaging 19 kg body weight was conducted at the Animal Health Research Farm of

Ricerca, Inc., Montville, Ohio by Dr. J. Szanto. The pigs were equally divided into two groups, each of which received a single dose of 15 mg tiamulin per kg body weight by stomach tube either as the soluble powder or as the liquid concentrate. Blood samples were taken at 0, 1, 2, 4, 5, 12, and 24 hours. The highest concentrations occurred at 4 hours for both formulations (C MAX = 1.26 µ g/mL for the soluble powder and 1.40 µ g/mL for the liquid concentrate). The differences in C MAX were not statistically significant. Likewise, the differences in areas under the curve (AUC) were not statistically significant (13.0 versus 11.5 for the liquid concentrate and soluble powder, respectively). The differences in T MAX, (3.65 versus 2.65), although statistically significant, are not biologically significant.

III. ANIMAL SAFETY

The safety of DENAGARD® (tiamulin) has been demonstrated in safety, efficacy, and field trials, which are discussed in the FOI Summaries for NADA 134-644 and 139-472 (48 FR 41384, September 15, 1983; 52 FR 26956, July 17, 1987).

In addition to the previously submitted studies with the technical (unformulated) and the water soluble (formulated) drug, an acceptability study using the liquid concentrate form was conducted at the Animal Health Research Farm of Ricerca, Inc., Montville, Ohio by Dr. J. Szanto. Twenty-four crossbred barrows and gilts weighing 25 to 34 kg each were medicated via drinking water using the liquid concentrate formulation to provide 60, 180, or 300 ppm tiamulin for 15 consecutive days. As tiamulin intake via medicated drinking water has been shown to be self-limiting (FOI Summary NADA 134-644), the highest level tested represents the maximum level pigs voluntarily consume before significantly restricting their water consumption. Average daily drug intakes were 6.6, 20.8 and 38.1 mg/kg body weight, respectively. No significant differences in weight gain or feed and drinking water consumption were observed. There were no signs of toxicity present. All 18 medicated pigs were necropsied. No treatment related gross pathological changes were found.

IV. HUMAN FOOD SAFETY

The Freedom of Information (FOI) Summary for original NADA 134-644, DENAGARD® Soluble Antibiotic (tiamulin soluble powder), describes toxicity, total residue, and metabolism studies that were done to establish the tolerance for tiamulin residues in edible swine tissues. [A notice of availability of that FOI Summary was published in the FEDERAL REGISTER on September 15, 1983 (48 FR 41384)]. No additional studies of those types were required for approval of DENAGARD® Liquid Concentrate, because the liquid concentrate is intended for dissolution in swine drinking water to achieve the same final tiamulin concentrations and doses approved for the soluble powder.

Thus, the tolerance established for tiamulin residues in swine remains at 0.4 part per million (ppm) of 8-*alpha*-hydroxymutilin in liver (21 CFR 556.738), and the regulatory methods remain as described in the Food Additives Analytical Manual on display in FDA's Freedom of Information Public Room.

The only human food safety study required for approval of the liquid concentrate was a marker residue depletion study to determine the withdrawal times for the new formulation. As noted above, the liquid concentrate formulation is intended for use at two doses, 3.5 mg tiamulin per pound of body weight (mg/lb BW) for treatment of swine dysentery, and 10.5 mg/lb BW for treatment of swine pneumonia. The soluble powder formulation is already approved for those same doses and indications.

The approach to determination of withdrawal times for the liquid concentrate was that, initially, a single residue depletion study would be done at the 10.5 mg/lb BW dose. If the liquid concentrate qualified for the same withdrawal time as the soluble powder at that dose, then a separate depletion study at the 3.5 mg/lb BW dose would not be required. The withdrawal time for the 3.5 mg/lb BW dose of the soluble powder would be assigned to the 3.5 mg/lb BW dose of liquid concentrate. The rationale is that if it can be demonstrated that the tissue residue depletion characteristics are essentially the same for the two formulations at the higher dose, then there is no reason to believe that this would not also be true at the lower dose. The withdrawal times assigned to the soluble powder formulation are 7 days for the 10.5 mg/lb BW dose and 3 days for the 3.5 mg/lb BW dose.

Marker Residue Depletion Study and Calculation of a Withdrawal Time

Twenty (20) crossbred, healthy pigs, weighing 58 to 80 pounds (average 69 pounds) were randomly assigned to five groups, consisting of two gilts and two barrows each. The pigs received the drug product at 10.5 mg tiamulin hydrogen fumarate per pound of body weight (23 mg/kg) for 5 consecutive days. The liquid concentrate, which in normal use will be diluted and administered in drinking water, was given by gavage to ensure that each pig received the desired dose.

The pigs were sacrificed by captive bolt stun gun and exsanguination, one group each, at withdrawal times of 2, 3, 4, 5, and 6 days.

The livers were removed from the animals and analyzed for the marker residue, 8-*alpha*-hydroxymutilin, using Fermenta's alternate determinative method. Both the original and alternate methods are gas chromatography procedures, and the alternate method differs from the original in only minor aspects (e.g., a megabore GC column was substituted for a packed column, using the same silicone liquid phase, and toluene was substituted for benzene). The alternate method has been reviewed and accepted by FDA.

The mean liver residue values, in parts per billion (ppb), and standard deviations at each time point are shown below in Table 1.

Table 1. Levels of 8-alpha-hydroxymutilin Marker Residue in Livers of Pigs Treated with Tiamulin Liquid Concentrate at 10.5 mg/lb BW for 5 days*

Withdrawal Time (days)	**Residues [ppb (+/- s.d.)**]**
2	645 (196)
3	313 (74)
4	202 (86)
5	167 (76)
6	115 (52)

* values in table are means of four pigs.
** s.d. = standard deviation

These residue depletion data were analyzed by a statistical method which determines the statistical tolerance limit for the 99th percentile of the population with 95% confidence. The analysis yielded a withdrawal time of 7 days for the 10.5 mg/lb dose of the liquid concentrate, which is the same withdrawal time approved for the soluble powder formulation. As noted above, this result supports assignment of a 3-day withdrawal time to the 3.5 mg/lb dose of the liquid concentrate, which is the withdrawal time assigned to the 3.5 mg/lb dose of the soluble powder.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that tiamulin liquid concentrate is effective against swine dysentery when administered in the drinking water for 5 days at a dose of 3.5 mg tiamulin per pound body weight, and is effective against swine pneumonia when administered in the drinking water for 5 days at a dose of 10.5 mg tiamulin per pound body weight.

A tolerance for the tiamulin marker residue, 8-*alpha*-hydroxymutilin, is established in swine at 0.4 ppm in liver (21 CFR 556.738). The presence of the marker residue at or below 0.4 ppm in liver will ensure that total tiamulin related residues will not exceed the respective safe concentrations of 3.6, 10.8, 14.4, and 14.4 ppm in swine muscle, liver, kidney, and fat.

A withdrawal period of 7 days has been assigned for the 10.5 mg/lb dose of the DENAGARD® (tiamulin) liquid concentrate formulation, based on the results of a residue depletion study done with the liquid concentrate at that dose. This withdrawal time is the same as is approved for the 10.5 mg/lb dose of the DENAGARD ® (tiamulin) soluble powder formulation. The fact that the two formulations have the same withdrawal time at the 10.5 mg/lb dose indicates that the depletion characteristics of the two formulations are essentially the same. There is no reason to believe that this would not also be true at the 3.5 mg/lb dose. Therefore, the 3-day withdrawal time assigned for the 3.5 mg/lb dose of the soluble powder has also been assigned to the 3.5 mg/lb dose of the liquid concentrate.

Labeling directions are adequate to enable laypersons to use this product to treat swine dysentery associated with *Treponema hyodysenteriae* and swine pneumonia associated with *Actinobacillus pleuropneumoniae*. Accordingly, this product has over-the-counter marketing status.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for marketing exclusivity, because new clinical or field investigations (other than bioequivalence or residue studies) were essential to the approval and conducted or sponsored by the applicant. DENAGARD ® is under patent numbers U.S. #3919290, #3987194, and #4278674; expiring November 11, 1992, October 19, 1993, and July 14, 1998, respectively.

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.