Approval Date: Nov 1 2001

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-192

Zeranol Long Acting (Ralgro® LA)

For increased rate of weight gain for up to 210 days in pasture cattle (slaughter, stocker, and feeder steers and heifers).

Sponsored by:

Schering-Plough Animal Health Corporation
1095 Morris Avenue
P. O. Box 3182
Union, New Jersey 07083

FREEDOM OF INFORMATION SUMMARY
FOR
RALGRO® LA (ZERANOL)

1. GENERAL INFORMATION

NADA Number: 141-192

Sponsor: Schering-Plough Animal Health Corp.
1095 Morris Avenue
PO Box 3182
Union, NJ 07083-1982

Generic Name: Zeranol

Trade Name: Ralgro® LA

Marketing Status: Over the Counter (OTC)

2. INDICATIONS FOR USE

For increased rate of weight gain for up to 210 days in pasture cattle (slaughter, stocker, and feeder steers and heifers).

3. DOSAGE FORM(S), ROUTE(S) OF ADMINISTRATION, AND RECOMMENDED DOSAGE

Dosage Form: Implantation

Route of Administration: Subcutaneous implantation in the middle of the posterior aspect of the ear.

Recommended Dosage: One implant containing 138 mg of zeranol. Each implant is made up of seven pellets with one pellet containing 18 mg of zeranol and six pellets containing 20 mg of zeranol per pellet.

4. EFFECTIVENESS

The new animal drug application contains data from adequate and well-controlled investigations demonstrating the effectiveness of Ralgro® L.A. for the indications for use and dosage as given in Sections **2** and **3** above.

Pivotal Studies:

The pivotal studies are dose titration studies in which the parameters measured are the same as those measured in field investigations. Four dose titration studies were conducted using a uniform protocol so that the results of the studies could be pooled and summarized. The four studies were conducted in major beef producing areas of the United States.

Name and Address of Investigators and Study Locations:

E. G. Johnson, D.V.M.
Johnson Research
24007 Hwy 20-26
Parma, Idaho 83660
Study Location: Parma, ID
Study #: 1920C-61-V97-370-01

Kent Haden, DVM
MFA Research
201 Ray Young Drive
Columbia, MO 66201-3599
Study Location: Marshall, MO
Study #: 1920C-61-V97-370-04

Dianne Hellwig, DVM, PhD
University of Arkansas
SW Research & Extension Center
362 Highway 174 North
Hope, AR 71801
Study Location: Hope, AR
Study #: 1920C-61-V97-370-02

Roger Sifferman, DVM
Bradford Park Veterinary Hospital
1255 E. Independence
Springfield, MO 65804
Study Location: Wheeler, TX
Study #: 1920C-61-V97-370-05

The purpose of the studies was to evaluate the dose response for zeranol long acting implants on rate of weight gain of steers and heifers maintained on pasture. The test animals were crossbred and purebred animals of various beef breeds. For each location, 175 steers and 175 heifers were maintained on the same pastures and allotted to treatments. Each calf was considered an experimental unit. The calves (5 treatments of 35 head/treatment/sex) were blocked by sex and weight (5 calves/weight block/sex) and implanted with either 0, 58, 98, 138, or 178 mg zeranol (long acting formulation). The calves weighed an average of 553 pounds when the studies were initiated. The duration of the studies was 175 days for the Arkansas study and 210 days for the remaining three studies.

Each calf was administered zeranol via subcutaneous implantation on the backside of the mid-ear. The control calves were sham implanted using an implant gun and needle. The calves were implanted only once at the initiation of each study.

Average daily gain (ADG) was calculated for day 175 (all studies) and for day 210 (all studies but Arkansas). The data for the day 175 ADG for the steers and heifers are summarized for each of the four dose titration studies in Table 1. The data for the day 210 ADG are summarized for the three longer studies in Table 2.

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 zeranol L.A. implants on average daily gain. For heifers, ADG was shown to be different among doses at the 0.0019 level of significance through day 175 and the 0.0017 level of significance through day 210. For day 175, ADG for doses 138 and 178 mg was significantly higher ($p<.05$) than the 0, 58 and 98 mg doses. For day 210, ADG for doses 98, 138 and 178 mg was significantly higher ($p<.05$) than the 0 and 58 mg doses. For steers, ADG was shown to be different among doses at the 0.0001 level of significance through both day 175 and day 210. For day 175, ADG for doses 98, 138 and 178 mg was significantly higher ($p<.05$) than the control group. For day 210, ADG for all doses was significantly higher ($p<.05$) than the control group.

TABLE 1: SUMMARY OF ADG FROM ALL FOUR DOSE TITRATION STUDIES COMPARING THE PERFORMANCE OF PASTURED STEERS AND HEIFERS ON VARIOUS LEVELS OF ZERANOL THROUGH DAY 175 OF THE STUDIES

Locations					
Zeranol (mg)	Idaho	Arkansas	Missouri	Texas	Pooled LS Means
Average Daily Gain (lbs) for Steers					
0	1.30	1.26	0.68	1.37	1.15
58	1.48	1.21	0.70	1.55	1.23
98	1.57	1.25	0.85	1.67	1.34
138	1.58	1.27	0.76	1.65	1.32
178	1.56	1.10	0.75	1.68	1.27
Average Daily Gain (lbs) for Heifers					
0	1.26	1.01	0.59	1.22	1.02
58	1.40	1.07	0.57	1.20	1.06
98	1.34	0.99	0.67	1.22	1.06
138	1.35	1.15	0.73	1.31	1.14
178	1.32	1.18	0.71	1.29	1.12

TABLE 2: SUMMARY OF ADG FROM THE THREE DOSE TITRATION STUDIES WITH DURATION OF 210 DAYS COMPARING THE PERFORMANCE OF PASTURED STEERS AND HEIFERS ON VARIOUS LEVELS OF ZERANOL

Locations				
Zeranol (mg)	Idaho	Missouri	Texas	Pooled LS Means
Average Daily Gain (lbs) for Steers				
0	1.20	0.74	1.66	1.20
58	1.35	0.74	1.83	1.30
98	1.43	0.89	1.94	1.42
138	1.44	0.82	1.88	1.38
178	1.46	0.79	1.94	1.39
Average Daily Gain (lbs) for Heifers				
0	1.24	0.52	1.50	1.09
58	1.34	0.55	1.55	1.15
98	1.32	0.60	1.57	1.16
138	1.34	0.65	1.64	1.21
178	1.32	0.65	1.63	1.20

5. TARGET ANIMAL SAFETY

The new animal drug application for Ralgro® L.A. references the target animal safety studies summarized in the FOI Summary for the related NADA 38-233 and provides a comparative implant study between Ralgro® Magnum and Ralgro® L.A. (See Section 6 below). The data from those studies demonstrate the safety of the new animal drug for the indications for use and dosage as given in Sections 2 and 3 above.

6. HUMAN FOOD SAFETY

A. Toxicity Studies:

Data regarding toxicity testing on zeranol are contained in the approved NADA 38-233.

B. Assignment of an Acceptable Daily Intake:

Tissue safe concentrations for total residue of zeranol have been established and codified under 21 CFR 556.760. These values were calculated using the now obsolete tissue consumption factors and thus, at this time, safe concentrations are deleted from the CFR and an Acceptable Daily Intake (ADI) is codified. The ADI for zeranol is 0.00125 mg/kg body weight/day (or, equivalently 0.075 mg/60 kg person per day). The ADI is calculated by dividing the NOEL of 0.125 mg/kg /day by the safety factor of 100.

C. Total Residue and Metabolism Studies

Studies on the metabolism of ^{3}H-zeranol in cattle have been summarized in a previous FOI Summary under NADA 38-233. The highest mean total tissue residue concentrations were found at 15 days in all tissues with liver containing the highest level (16 ppb). At all slaughter times after implantation with 32 and 72 mg of zeranol, residues in all edible tissues were far below the respective safe concentrations.

D. Comparative Implant Study

In support of a new formulation containing zeranol at an increased dose, the issue of tissue residues was addressed by use of an explant payout study. The payout rate of zeranol long acting (ZLA) pellets was compared to that of Ralgro® Magnum (RM) implants in a study conducted by Schering-Plough Animal Health in Williamsburg, KS. Residual zeranol in ZLA and RM pellets explanted from cattle (180 crossbred beef calves 4-6 months old) was measured by Schering-Plough Physical Analytical Chemistry Research and Development in Mundelein, Illinois (initial validation and samples through Day 70) and Schering-Plough Research Institute, Kenilworth, NJ (all other samples). The ZLA dose used in the residue study was 178 mg; 138 mg is the intended market dose of the ZLA implant (Table 3).

Table 3.
Mean zeranol (mg) remaining in implant and percent of initial dose remaining in implants

	ZLA treatment (178 mg)				RM treatment (72 mg)			
Day	Mg Zeranol	STD	% Zeranol	STD	Mg Zeranol	STD	% Zeranol	STD
0	171.4	5.7	96.3	3.2	67.0	3.8	93.1	5.3
35	143.6	9.1	80.7	5.1	41.8	6.3	58.1	8.7
70	108.9	17.0	61.2	9.6	17.2	8.3	23.9	11.5
105	71.4	18.2	40.1	10.2	2.5	4.0	3.4	5.6
140	53.6	11.9	30.1	6.7	0.0	0.1	0.0	0.1
175	41.2	25.1	23.2	14.1	0.0	0.0	0.0	0.0
210	42.6	20.9	24.0	11.7	0.0	0.0	0.0	0.0
245	17.6	19.7	9.9	11.1	0.0	0.0	0.0	0.0

The ZLA implant was explanted at 35 day intervals up to 245 days with 10 heifers and 10 steers comprising the time point groups. The ZLA implant (178 mg) released 0.79 mg/day through Day 175 and then the dose rate dropped to 0.34 mg/day. The zeranol payout rate from the RM implant was linear at 0.71 mg/day from Day 0 through Day 70 and can be extrapolated through Day 105. Statistical comparison showed that the initial release rate of the ZLA implant was similar to the release rate of the RM implant (Table 4).

Table 4.
Zeranol Release in mg per 35-day Interval

Interval	ZLA formulation (178 mg)		RM formulation (72 mg)	
	Subtraction of Means	Linear Regression	Subtraction of Means	Linear Regression
Day 0 → 35	27.8	27.6	25.2	24.9
Day 35 → 70	34.7	27.6	24.6	24.9
Day 70 → 105	37.5	27.6	14.7	24.9
Day 105→140	17.8	27.6	2.5	0
Day 140→175	12.4	27.6	0	0
Day 175→205	(+1.4)	12.0	0	0
Day 205→245	25.0	12.0	0	0

This study demonstrates that the payout rate of ZLA implants (178 mg) does not exceed that of the currently approved RM (72 mg) implants. The safety of the RM implants previously has been demonstrated under NADA 38-233.

E. Tolerance for the Marker Residue

From the total residue study conducted under NADA 38-233 it was determined that neither a tolerance for a marker residue nor a regulatory assay was needed for ZLA.

F. Withdrawal Period

From the total residue study conducted under NADA 38-233 and the payout data in this application, it was determined that ZLA qualifies for a zero withdrawal.

G. Regulatory Method

Since a withdrawal period is not required for the use of ZLA, neither a regulatory or confirmatory method was required for this approval. Methods for detection of zeranol in cattle tissue are on file at the Center for Veterinary Medicine, US Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, MD 20855.

7. 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 demonstrate that a 138 mg zeranol implant when used for up to 210 days in pasture cattle (slaughter, stocker, and feeder steers and 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 layman have been provided and the product will have over-the-counter marketing status.

As part of this approval, the human food safety information is updated and an Acceptable Daily Intake (ADI) of 0.00125 mg/kg body weight/day is codified. The payout rate data of the long acting implant indicate that daily exposure will not be greater than with the approved zeranol products under NADA 38-233.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the use of the product (Ralgro® LA implant) containing 138 mg zeranol for which the application was approved.

8. LABELING

Three (3) pages of labeling are attached as follows:

1. Box Label
2. Package Insert (front)
3. Package Insert (back)