FREEDOM OF INFORMATION SUMMARY
FOR
RALGRO® MAGNUM (ZERANOL)

1. GENERAL INFORMATION

NADA Number: 38-233

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

Generic Name: Zeranol

Trade Name: Ralgro® Magnum

Marketing Status: Over the Counter (OTC)

Effect of Supplement: This supplement provides for the use of an ear implant containing 72 mg zeranol in steers fed in confinement for slaughter for improved feed efficiency.

2. INDICATIONS FOR USE

For increased rate of weight gain and improved feed efficiency in steers fed in confinement for slaughter.

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

Dosage Form: Implantation

Route of Administration: Subcutaneous implantation on the posterior aspect of the ear.

Recommended Dosage: One implant containing 72 mg of zeranol. Each implant is made up of six pellets with each pellet containing 12 mg of zeranol.

4. EFFECTIVENESS

The supplemental new animal drug application contains data from adequate and well-controlled investigations demonstrating the effectiveness of Ralgro® Magnum 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 parameters as are 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:

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The purpose of the studies was to evaluate the dose response for zeranol on average daily weight gain and feed efficiency of steers fed in confinement for slaughter. The test animals were cross-bred animals of English and Exotic breeds. For each study, 256 to 523 steers (depending on study location) were assigned to pens (8 to 19 steers/pen depending on location) and allotted to treatments via a completely randomized design. Each treatment was replicated 4 to 5 times (4 to 5 pens/treatment) depending on location. The treatments consisted of 0, 24, 36, 48, 60, 72, 84, and 96 mg zeranol. The steers weighed approximately 715 pounds when the studies were initiated. The duration of the studies ranged between 119 and 143 days.

Each steer was administered zeranol via subcutaneous implantation on the backside of the mid-ear. The control steers were not implanted. The steers were administered zeranol once at the initiation of each study.

Average daily gain (ADG) and feed/gain (F/G) data for the steers are summarized in Table 1 for each of the four dose titration studies.

A combined statistical analysis (analysis of variance) of the data from the four studies was conducted for ADG and F/G. ADG showed differences among doses at the 0.0007 level of significance. All doses 36 mg and higher performed significantly higher in ADG than the 0 mg dose at a significance of 0.0046 or lower (one-sided). The 24 mg dose did not elicit a significant improvement in ADG ($p<0.09$) level. Animal performance at the 72 mg level was significantly higher for ADG than that of the 24, 36, and 60 mg doses, with a p-value of no greater than 0.0230. The 72 mg level showed an improvement in ADG over the 48 mg dose only at the 0.11 level, and demonstrated no difference in ADG from either the 84 or 96 mg dose at a level higher than 0.25 (two-sided).

F/G responses to the various doses demonstrated significant differences at the 0.0347 level. The 48, 60, 72, and 96 mg doses resulted in lower F/G than the 0 mg dose at a significance level of 0.047 or lower. The 48 mg dose showed no significant improvement over either the 24 or 36 mg doses ($p>0.148$). F/G performance at the 72 mg dose was significantly improved compared to the 24, 36, and 84 mg levels ($p=0.018$).

Linear-plateau models were fitted to the adjusted mean responses for the pooled data, and the optimal doses for ADG and F/G were identified as 72 mg and 48 mg, respectively.

No dose related effects were noted in carcass quality or liver abscess scores.

TABLE 1. SUMMARY FROM FOUR DOSE TITRATION STUDIES COMPARING THE PERFORMANCE OF CONFINED STEERS ON VARIOUS LEVELS OF ZERANOL

	Locations				
Zeranol (mg)	Idaho	Kansas	Illinois	Colorado	Pooled LS Means
Average Daily Gain (lbs)					
0	3.08	3.37	2.81	3.01	3.07
24	3.13	3.50	3.00	3.00	3.16
36	3.49	3.62	2.94	2.96	3.25
48	3.43	3.68	2.96	3.20	3.32
60	3.34	3.63	2.99	3.08	3.26
72	3.59	3.75	3.20	3.06	3.40
84	3.41	3.54	3.20	3.15	3.32
96	3.53	3.65	3.10	3.19	3.37
Feed/Gain (lbs dry matter/lb gain)					
0	6.46	6.39	6.68	7.00	6.57
24	6.64	6.27	6.06	6.94	6.48
36	6.28	6.13	6.28	7.18	6.47
48	6.38	6.22	6.05	6.88	6.38
60	6.43	6.16	6.06	7.00	6.41
72	6.19	6.02	6.07	6.79	6.27
84	6.74	6.38	6.08	6.90	6.52
96	6.29	6.16	6.14	6.72	6.34

5. TARGET ANIMAL SAFETY

Target animal safety is established by the data in the parent application. Therefore, no further studies were required.

6. HUMAN FOOD SAFETY

Human food safety is established by the data in the parent application. Therefore, no further studies were required.

7. AGENCY CONCLUSIONS

Adequate data is established to demonstrate the safe and effective use of RALGRO® MAGNUM (ear implant containing 72 mg zeranol) when used in steers fed in confinement for slaughter for improved feed efficiency.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the use of an ear implant containing 72 mg zeranol in steers fed in confinement for slaughter. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug.

8. LABELING

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

1. Carton Label
2. Package Insert - (front)
3. Package Insert - (back)