Date of Approval Letter: May 16, 2001

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 136-742

CURATREM®

(clorsulon)

"…establishing residue tolerance in muscle of cattle"

Sponsored by :

Merial Ltd.

2100 Ronson Rd.

Iselin New Jersey 08830-3077

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I. GENERAL INFORMATION

NADA Number:	136-742
Sponsor:	Merial Ltd., 2100 Ronson Rd., Iselin, NJ 08830-3077
Generic Name:	Clorsulon
Trade Name:	CURATREM® suspension oral drench
Marketing Status:	OTC (Over-the-Counter)
Effect of Supplement:	This supplement provides for the revision of 21 CFR 556.163 by the addition of tolerance in muscle of cattle and acceptable daily intake (ADI) and deletion of safe concentrations.

II. INDICATIONS FOR USE

For the treatment of immature and adult liver fluke (*Fasciola hepatica*).

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

A. Dosage Form

Oral suspension (drench)

B. Route of Administration

Oral

C. Recommended Dosage

1/4 fl. oz. per 200 lb or 75 mL per 200 lb (91 kg)

IV. EFFECTIVENESS

See the original Freedom of Information (FOI) Summary for NADA 136-742.

V. ANIMAL SAFETY

See the original FOI Summary for NADA 136-742.

VI. HUMAN SAFETY

A. Human Food Safety Studies and Safe Concentrations of Residues

The basic toxicology and residue chemistry studies that support the use of clorsulon in cattle are summarized in the FOI Summary for the original approval of NADA 136-742 (CURATREM®). An ADI of 8 micrograms per kg of body weight per day and the safe concentrations for total residues listed below were assigned for residues of clorsulon in cattle on the basis of the toxicology studies. The residue and metabolism studies established 1 ppm as the tolerance for residues of parent clorsulon (the marker residue) in cattle kidney (the target tissue).

Tissue	Safe Concentration (ppm)
Muscle	1
Liver	2
Kidney	3
Fat	4

B. Assignment of a Muscle Tolerance

A muscle tolerance of 100 ppb parent clorsulon was assigned following a review of the residue studies with clorsulon in cattle that have been submitted to NADA 136-742 and NADA 140-833. The residue and metabolism data in study RN-209 showed that unchanged clorsulon represents approximately 40% (approximately 54 ppb) of the total residue in muscle at 7 days post dosing as determined by reverse isotope dilution analysis. Those results confirm that parent clorsulon can serve as the marker residue in muscle tissue in cattle.

The value of 100 ppb as the tolerance for clorsulon in cattle muscle was chosen following a statistical analysis of the muscle residue depletion data of clorsulon in studies No. CA-173 and CA-187 that are described in the FOI Summary for the original approval of NADA 136-742. The mean residue values from those studies are listed in Table 1, below.

Table 1. Residue levels (ppb) of parent clorsulon measured by gas chromatography in muscle tissue of cattle dosed with a single 10 mg per kg body weight oral dose of clorsulon as an oral suspension.

Days Post-Dosing	Clorsulon in Muscle (ppb)
3	140
5	52
7	18
10	7
14	4
21	2
28	2

The upper tolerance limit (99% and 95% confidence) for clorsulon in muscle at eight days post dosing (the withdrawal time for CURATREM®) was calculated to be 82 ppb. That value was rounded up to 100 ppb for the muscle tolerance assignment.

The choice of 100 ppb as the tolerance for clorsulon in cattle muscle makes it possible to identify animals that have been treated with CURATREM® (clorsulon) and slaughtered within a week of treatment. Residues of clorsulon in cattle muscle are not indicative of the safety of residues in other edible tissues.

VII. AGENCY CONCLUSIONS

The information submitted in support of this supplemental application satisfy the requirements of Section 512 of the Federal Food, Drug and Cosmetic Act (FFDCA) and implementing regulations at Part 514 of Title 21 of the Code of Federal Regulations (21 CFR 514), to enable FDA to revise 21 CFR 556.163 to establish a tolerance for residues of clorsulon in cattle muscle.

The ADI for clorsulon is established at 0.008 mg/ per kg per day as published in the original FOI Summary for NADA 136-742. The value of 100 ppb parent clorsulon is assigned as the tolerance for unchanged clorsulon in cattle muscle. That tolerance was based on residue and metabolism data submitted with the original NADA 136-742 for the oral drench formulation of CURATREM® (clorsulon). The safe concentrations of clorsulon remain unchanged by this supplement. However, the safe concentrations are being deleted from 21 CFR 556.163 because the agency no longer codifies safe concentrations, and relies upon the tolerance in specific edible tissues to determine safe/unsafe residues. The pre-slaughter withdrawal period of 8 days in cattle remains unchanged.

There is reasonable certainty that the directions for use on labeling can and will be followed in practice. Accordingly, the Agency has concluded that this product shall retain over-the-counter marketing status.

In accordance with 21 CFR 514.106(b)(2)(xi) this is a Category II change corresponding to a change in the tolerance of residues that did not require a re-evaluation of the safety and effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals does not qualify for marketing exclusivity because the supplemental application does not contain new clinical or field investigations (other than bioequivalence or residue studies), and new human food safety studies (other than bioequivalence or residue studies) essential to the approval and conducted or sponsored by the applicant.

The Agency has carefully considered the potential environmental effect of this action and has concluded that the action qualifies for a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.33(a)(1).

VIII. Approved Product Labeling

See original FOI Summary for approved labeling.

Copies of applicable labeling may be obtained by writing to:

Freedom of Information Office
Center for Veterinary Medicine, FDA

7500 Standish Place
Rockville, MD 20855