

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 128-409

B. Sponsor

MERCK & CO., INC.
P.O. Box 2000, WBC-130
Rahway, New Jersey 07065-0914

C. Proprietary Name

IVOMEK® Injection for Cattle

D. Established Name

Ivermectin

E. Dispensing Status

OTC

F. Indication

IVOMEK® 1% injection for cattle is indicated for the treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, grubs, lice, and mange mites of cattle.

Gastrointestinal Nematodes (Adults and Fourth-stage larvae): *Haemonchus placei*, *Ostertagia ostertagi*, *O. lyrata*, *Trichostrongylus axei*, *Cooperia oncophora*, *T. colubriformis*, *C. punctata*, *C. pectinata*, *Oesophagostomum radiatum*, *Nematodirus helvetianus*, *N. spathiger* (adults only)

Lungworms (Adults and Fourth-stage larvae): *Dictyocaulus viviparus*

Grubs (First, second and third instars): *Hypoderma bovis*, *H. lineatum*

Lice: *Linognathus vituli*, *Haematopinus eurysternus*

Mites: *Psoroptes ovis* (Syn. *P. comunis* var. *bovis*), *Sarcoptes scabiei* var. *bovis*

G. Effect of Supplement

New tolerance for residues of ivermectin B1a in cattle liver of 100 ppb and revised safe concentration in tissues.

II. EFFECTIVENESS

As discussed in the parent NADA 128-409 FOI summary (Approval date February 13, 1984).

III. TARGET ANIMAL SAFETY

As discussed in the parent NADA 128-409 FOI summary (Approval date February 13, 1984).

IV. HUMAN FOOD SAFETY

A. Toxicity Tests

Toxicity tests determining the human food safety of IVOMEK® (ivermectin) Injection for cattle are included in the Freedom of Information summary for this NADA (approval date, February 13, 1984). A detailed summary of these studies has been published (*Ivermectin and Abamectin*, Campbell, W.C. (ed.) Springer-Verlag, New York, 1989). Additional toxicity information provided in this supplemental NADA is summarized below:

1. Studies Conducted in Healthy Volunteers.

Four pre-clinical studies were performed with ivermectin to determine the therapeutic dose, bioavailability, metabolism and pharmacokinetics in humans. These studies, while designed to obtain specific information listed in the study objective, also provided useful human safety observations which were summarized under the heading "Safety Report". These subjects were closely monitored in a hospital throughout the studies for signs and symptoms of adverse experiences. Physical examinations were conducted pre- and post-treatment. Vital signs, including blood pressure, pulse and respiratory rate were measured before and at frequent intervals post-dosing. Hematological evaluation included: hemoglobin, hematocrit, total white blood count, differential white blood count and platelet count. Blood chemistry included: SGOT, SGPT, alkaline phosphatase, total bilirubin, LDH creatinine, BUN, blood sugar, total protein, albumin and globulin.

Urinalysis included: protein, sugar, red blood cells, white blood cells and epithelial cells. There were no adverse clinical experiences reported and laboratory values were all within normal ranges.

2. A Multiclinic, Double Blind Study of Ivermectin (MK-933) and Placebo in Patients with Onchocerciasis. Study # 5003 Protocol # 519-00

Investigators:

Dr. B. Green, M.D.
Case Western Reserve and the Uniroyal Rubber Plantation
Liberia

Professor M. Lariviere, M.D.
University of Paris and Odienne Hospital
Ivory Coast

Drs. Schulz-Key, Ph.D. and G. Helling, M.D.
Institute of Tropical Medicine
Tuebingen, W. Germany and Sokode, Togo
Dr. K. Awadzi
Tamale Hospital
Ghana

Dr. P. Vingtain, M.D.
Institut D'Ophtalmologie

Tropical D'Ophthalmologie
Bamako, Mali

Dr. G. Zea-Flores, M.D.
Roosevelt Hospital
Guatemala City, Guatemala

Objective: To document, in onchocerciasis patients, the safety and efficacy of treatment with ivermectin.

Study Design: A multicenter, double-blind, randomized, placebo controlled study comparing three doses of ivermectin (100, 150 and 200 µg/kg). Enrollment criteria specified hospitalized male and female patients, 12 to 60 years of age with moderate or severe infections with *Onchocerca volvulus* but otherwise in good health. Patients were monitored, in hospital, for adverse signs. Safety endpoints included ophthalmologic examinations, physical examinations, hematology, blood chemistry and urinalysis. A total of 1278 patients were treated as follows: ivermectin at 100 µg/kg (319), 150 µg/kg (322), 200 µg/kg (322), placebo (315).

Safety Report: All doses of ivermectin were well tolerated. As expected, adverse reactions related to microfilarial death were common. Overall, 47.6 to 52.8% of persons in the treatment groups, and 29.8% of persons in the placebo group showed clinical adverse experiences. None of these were considered serious, and no persons were discontinued from the study. There was an episode of transient hypotension in a person taking anti-hypertensive therapy and chloroquine, not thought to be drug-related, and an isolated episode of possible hypoglycemia.

3. An open study of the Tolerability, Safety and Efficacy of Single Oral 150 µg/kg doses of ivermectin (MK-933) in children 5 to 12 years of age with onchocerciasis.

Study # 5544, Protocol # 545-00

Investigator: Professor M. Lariviere, M.D., University of Paris.

Site: Odienne Hospital, Ivory Coast

Objective: To investigate, in children 5 to 12 years of age and infected with *O. volvulus*, the tolerability, laboratory and clinical safety, and efficacy of a single oral dose (150 mg/kg) of ivermectin.

Study Design: An open study in male (n=71) and female (n=32) children with onchocerciasis and otherwise in good health. All patients were hospitalized for at least seven days following administration of ivermectin and monitored for adverse signs. Safety endpoints included ophthalmologic examination, physical examination, hematology, blood chemistry and urinalysis.

Safety Report: Ivermectin was well tolerated. The most common clinical experience was headache and myalgia. No clinical adverse reactions were considered serious and no laboratory adverse experiences were reported.

4. Signs of ivermectin toxicosis in man.

Results of accidental overdosing with ivermectin - containing veterinary products suggest that the acute signs and symptoms of ivermectin intoxication in man are similar to those observed in laboratory animals, however, the doses required to elicit these signs are higher in man.

Ivermectin Adverse Reactions Database

Clinical Summaries Case Report # 00014493.

A two-year old male ingested a quantity of IVOMEK® injectable formulation for cattle (10 mg/ml of ivermectin) and received an estimated ivermectin dosage of approximately 6-8 mg/kg. The patient exhibited drowsiness, ataxia, vomiting, mydriasis, right bundle branch block, ventricular ectopy and weakness. The child recovered with no apparent after effects.

Clinical Summaries Case Report # 00052048.

A 16-year old male was reported to have ingested 11.5 ml of the IVOMEK® Injectable formulation for cattle. Symptoms included mydriasis, vomiting, pallor, tachycardia, somnolence, variable blood pressure and urticaria. On follow-up, the patient was noted to have recovered from all symptoms with the possible exception of urticaria. Exposure was estimated at 115 mg total dose or 10X the therapeutic human dose of ivermectin.

B. Safe Concentration Of Residues

The safe concentration for drug residues represents the amount of drug, parent and metabolites, which can be consumed daily throughout a lifetime.

Allowable Daily Intake

These human studies support the findings of the laboratory animal toxicity studies with ivermectin that indicate that the primary human food safety concern for ivermectin is related to its neurotoxic effects. The human clinical database on ivermectin also indicated that the mouse teratology study, which was used to establish the safe concentration in the original approval, is not the most appropriate model for this calculation. Considering the results of the standard battery of toxicology studies conducted with ivermectin, and the information obtained in the human studies, the 90-day dog study with a NOEL of 0.5 mg/kg/day for neurotoxicity is a more appropriate study for establishing the safe concentration for ivermectin.

The subchronic and chronic effects of ivermectin were quantitatively similar. Therefore, the 1000-fold safety factor, which is generally applied to the 90-day studies to extrapolate to chronic exposure, is inappropriate. Rather, a 500-fold safety factor is assigned to the NOEL of 0.5 mg/kg/day obtained in the 90-day dog study. The new ADI for ivermectin is 0.5 mg/kg/day divided by 500 or 1 µg/kg/day.

Safe Concentration

A safe concentration in muscle of cattle is calculated from the acceptable daily intake; assuming the average weight of man to be 60 kg and the daily human intake of muscle to be 500 grams.

Safe concentration in muscle = (60 kg) (1 µg/kg/day) / 500 g/day = 120 ppb

The safe concentration of residues in liver, kidney and fat are derived from this number using appropriate food consumption values (food factors) for these tissues:

Liver: 120 ppb X 2 (food factor) = 240 ppb

Kidney: 120 ppb X 3 (food factor) = 360 ppb

Fat: 120 ppb X 4 (food factor) = 480 ppb

Injection Site

Ingestion of an entire injection site from an IVOMEK-treated animal is considered an unlikely event. The human food safety assessment of injection site exposures is based on acute toxicity of ivermectin. Clinical studies conducted in healthy non-parasitized volunteers demonstrate that a 15 mg oral dose of ivermectin is well tolerated. Applying a ten-fold safety factor to this 15 mg oral dose and a consumption value of 500 grams results in a safe concentration of 3 ppm at injection sites

C. Metabolism And Total Residue Depletion Studies

Section 6.C. of the Freedom of Information Summary issued at the time of approval (February 13, 1984) of IVOMEK® (ivermectin) Injection for cattle describes metabolism of 3H labeled MK-933 in cattle, comparative metabolism in rats and total residue depletion from edible tissues. No additional total residue depletion or metabolism studies were provided in this supplement. Residue data generated in radiolabeled study RN-190 was used to recalculate the tolerance (See Below).

D. Recalculation Of The Tolerance

The residue data generated in RN-190 was used to calculate the tolerance for residues of ivermectin H2B1a (marker substance) in cattle liver (marker tissue) based upon a safe concentration of 240 ppb for total residues of ivermectin. Based upon results of that study, ivermectin Bla represents approximately 42 percent of the total ivermectin residues in liver when residues are at the safe concentration of 240 ppb. The tolerance for the marker residue derived from that relationship is 100 ppb (42 percent of 240 ppb = 100.8 ppb).

E. Studies Demonstrating A Withdrawal Period

A tissue residue depletion study (ASR 13527) was conducted to determine the marker residue (H2Bla) concentrations in edible tissues of cattle at times following treatment with IVOMEK® injection for cattle injected subcutaneously at the recommended use level. Crossbred, beef type cattle, aged 12-14 months and weighing between 287 and 401 kg were used. Six male castrates and six females were slaughtered on each of days 21, 28, 35, 42, 49 and 56. Six untreated cattle (3 male castrates, 3 females) served as controls. Marker residue assays were conducted on liver tissue and injection site samples using the high performance liquid chromatography fluorescence determinative assay method.

Average marker residue concentrations in samples were:

ppb Found

Days Withdrawal	Liver	Injection Site
21	46 ± 37	NA
28	27 ± 16	1280 ± 2979
35	10 ± 10	576 ± 817
42	3 ± 3	570 ± 1037
49	3 ± 4	231 ± 724
56	NA	NA

NA: Not assayed

Statistical analysis of the residue depletion data generated in ASR 13527, using the tolerance of 100 ppb in liver, yields a withdrawal period of 34 days. However, the **official withdrawal** period is set at **35 days** as the 35-day sacrifice group in study 13527 was the first group in which all injection site residues were below the safe concentration (3 ppm) assigned for residues of ivermectin at the injection site.

V. AGENCY CONCLUSIONS

The data submitted in support of this supplement satisfy the requirements of Section 512 of the Federal Food, Drug and Cosmetic Act (FFDCA). Based on the additional toxicology data submitted, the tolerance for ivermectin Bla in cattle liver has been changed from 15 ppb to 100 ppb and a 35-day withdrawal period in cattle has been calculated.

Although the human data are limited to acute (therapeutic/accidental) exposure to ivermectin, it appears that neurotoxicity is the endpoint of toxicological concern. The agency established the drug's safe concentration on the animal model which was the best predictor of this toxic endpoint.

Under the Center's supplemental approval policy [21 CFR 514.106(b)(2)], this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation 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 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.