Approval Date: November 18, 1996

# FREEDOM OF INFORMATION SUMMARY

## 1. GENERAL INFORMATION

**NADA Number:** 140-988

**Sponsor:** Merck Research Laboratories
Division of Merck & Co., Inc.
P. O. Box 2000
Rahway, New Jersey 07065-0914

**Established Name of Drug:** Ivermectin

**Trade Name:** IVOMEC® SR Bolus for Cattle

**Marketing Status:** OTC

## 2. INDICATIONS FOR USE

**NEMATODES**

The IVOMEC® SR Bolus is indicated for the treatment of established infections and, throughout its approximately 135-day ivermectin delivery period, prevents the establishment of infection by newly ingested larvae of the following nematode species:

Gastrointestinal Roundworms

*Haemonchus placei*
*Ostertagia ostertagi*
*Trichostrongylus axei*
*Trichostrongylus colubriformis*
*Cooperia* spp.
*Nematodirus helvetianus*
*Bunostomum phlebotomum*
*Oesophagostomum radiatum*

Lungworms

*Dictyocaulus viviparus*

IVOMEC® SR Bolus controls established infections with hypobiotic (inhibited) fourth-stage larvae of *Ostertagia ostertagi*.

**MANGE MITES**

Established infestations of the following mange mites are controlled.

*Psoroptes ovis*
*Sarcoptes scabiei*

**SUCKING LICE**

Established infestations of the following sucking lice are controlled.

*Linognathus vituli*
*Solenopotes capillatus*

**CATTLE GRUBS**

Initially, control is provided against migrating *Hypoderma* larvae or grubs acquired prior to administration of the IVOMEC SR Bolus; thereafter, prophylaxis is provided for approximately 135-days against newly acquired larvae.

*Hypoderma* spp

**TICKS**

Control of the following tick will be provided by interfering with engorgement with blood and completion of the reproductive portion of the life cycle by newly acquired young adult females during the period of ivermectin delivery. However, larvae, nymphs and adult males, as well as young adult females already on the host at the time of treatment and actively in the engorgement process, may not be visibly affected.

*Amblyomma americanum*

## 3. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

The product is for use in ruminating cattle at least 12 weeks of age and weighing at least 275 lb (125 kg) and not more than 660 lb. (300 kg) body weight on the day of administration. Each animal will receive one bolus formulated to deliver 12 mg of ivermectin/day for 135 days, administered orally. Each bolus contains 1.72 g ivermectin.

## 4. EFFECTIVENESS

A clinical development program including dose determination, dose confirmation and clinical field trial investigations support the safety of the IVOMEC SR Bolus and efficacy against a range of important endo- and ectoparasites.

In all clinical studies, the results from the bolus-treated group(s) were compared with results from an untreated or placebo-treated control group. Each claim for a parasite species is supported by at least two controlled studies. Efficacy is expressed as percentage (%) reduction compared to controls calculated as follows:

$$\% \text{ Reduction} = \frac{AM_C - AM_T}{AM_C} \times 100$$

where $AM_C$ = Arithmetic mean number of parasites in control cattle
$AM_T$ = Arithmetic mean number of parasites in treated cattle

The IVOMEC SR Bolus provided greater than 90% efficacy for each endo- and ectoparasite claim. Data from the development program support the use of the IVOMEC SR Bolus for treatment and prophylactic control of important gastrointestinal and pulmonary nematodes as well as certain arthropod parasites for 135 days after administration.

### Overview of the Development of the IVOMEC® SR Bolus

Several different devices were utilized in the development of the IVOMEC SR Bolus. Dose titration trials (studies ASR 13469, 13470 and 11170) were conducted using ALZET osmotic pumps. Each study included groups of cattle treated with two to five dose levels in the range of 2.5 to 44 μg/kg/day. Based on these studies a dose of 12 mg of ivermectin per day was selected which is equivalent to 96 to 40 μg/kg/day for cattle weighing 125 to 300 kg on the day of treatment. Some dose confirmation studies were conducted with an early version of the SR bolus, designated as Prototype 3B, which delivered ivermectin at the selected dose for approximately 90 days. The device was modified to extend the duration of drug delivery to approximately 135 days while maintaining the dose of ivermectin delivered at 12 mg/day. The dose confirmation program was completed using this modified device which was designated as Prototype 5APT or the commercial device. To compare the rate of ivermectin delivery from the two prototypes, plasma ivermectin concentrations were determined in animals treated with a 3B or 5APT device.
On Day 28 and 56 of delivery, mean ivermectin concentrations were comparable for cattle treated with either of the prototypes. Three clinical trials conducted using the commercial 5APT SR bolus produced blood levels that are comparable to previous

prototypes and the proposed delivery period of approximately 135 days was achieved. These levels of ivermectin were adequate to treat and prevent the infection by the internal and external parasites listed on the labeling.

## A. Dose Selection

Dose selection studies were conducted to determine the dose level of ivermectin administered by sustained ruminal delivery that would control endo- and ectoparasites in cattle. There were three studies, one with endoparasites and two with endo- and ectoparasites. Each study included a group of placebo-treated control cattle and groups of cattle treated with two to five dose levels in the range of 2.5 to 40 μg/kg/day. The drug was administered by Alzet osmotic pumps (Alza Corp., Palo Alto, CA) which were designed to release an aqueous formulation of ivermectin continuously for approximately 30 days. The dose of ivermectin delivered was determined by the concentration of drug in the aqueous formulation and the number of pumps given to each animal.

1. Study ASR 13469 was conducted in the USA to determine the optimum dose level of ivermectin delivered intraruminally to prevent the establishment of newly acquired infective nematode larvae. Twenty-four calves were allocated by restricted randomization on breed, sex and body weight to six treatment groups. Cattle in one group acted as placebo-treated controls while those in the other five groups were given Alzet pumps delivering ivermectin at nominal dose levels of 2.5, 5, 10, 20 or 40 μg/kg/day (calculated actual mean dose levels were 2.5, 4.3, 9.2, 21.5 and 40.3 μg/kg/day). Treatments were administered on Day 0. Doses were individually tailored to the weight of each calf by varying the concentration of ivermectin in the formulation used to fill each pump.

   Infective third-stage larvae ($L_3$) of gastrointestinal nematode species were administered on Days 7, 9, 11, 14, 16, 18, 23, 25 and 28 after treatment and lungworms on Days 25 and 28. The following parasites were administered: *H. placei, O. ostertagi, T. axei, D. viviparus, T. colubriformis, C. oncophora, C. punctata, N. helvetianus, O. radiatum,* and *A. americanum*. The calves were necropsied for nematode recovery between Days 49 and 52. There were no adverse reactions to treatment. For two parasites, *Trichostrongylus colubriformis* and *Nematodirus helvetianus,* adequate infections did not establish in control animals but did establish in animals given the lowest dose of ivermectin.

   The count from this ivermectin-treated group was used as the "control" nematode burden for calculation of percentage reduction for the higher ivermectin dose levels. Nematode counts and percentage reductions are summarized below.

**<u>Arithmetic Mean Nematode Counts and Percentage Reduction</u>**

| | | Ivermectin (µg/kg/day) | | | | |
|---|---|---|---|---|---|---|
| **Nematode** | **Control** | **2.5** | **4** | **9** | **22** | **40** |
| *Haemonchus placei* | 1793 | 96% | 89% | >99% | 100% | 100% |
| *Ostertagia ostertagi* | 5965 | 94% | 95% | >99% | 100% | >99% |
| *Trichostrongylus axei* | 3140 | 80% | 96% | 100% | 100% | 100% |
| *Trichostrongylus colubriformis* | - | 1940 | 96% | >98% | 100% | 100% |
| *Cooperia oncophora* | 1665 | 31% | 56% | >99% | 100% | 100% |
| *Cooperia punctata* | 3418 | 85% | 88% | >99% | 100% | 100% |
| *Nematodirus helvetianus* | - | 503 | 45% | 72% | 90% | 100% |
| *Oesophagostomum radiatum* | 150 | 100% | 100% | 100% | 100% | 100% |
| *Dictyocaulus viviparus* | 137 | 100% | 100% | 100% | 100% | 100% |

Efficacy against the cattle tick, *Amblyomma americanum* was also investigated in control calves and calves treated at the highest ivermectin dose level (40 µg/kg/day). Twenty-five adult pairs of *A. americanum* were applied to each animal on Day 10. Detaching females were collected each day and incubated for oviposition. Based on mean weight of eggs produced, ivermectin at 40 µg/kg/day provided 100% control of *A. americanum*.

Investigator: Dr. J. R. Egerton
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2. Study ASR 13470 was conducted in the USA to determine the optimum dose level of ivermectin delivered intraruminally to prevent the establishment of newly acquired infective nematode larvae. Twenty calves were allocated by restricted randomization on sex and body weight to four treatment groups. Cattle in one group acted as placebo-treated controls while those in the other three groups were given Alzet pumps delivering ivermectin at nominal dose levels of 15, 22 or 30 μg/kg/day (calculated actual mean dose levels were 16.6, 24.4 and 33.7 μg/kg/day). Treatments were administered on Day 0. Infective nematode $L_3$ were administered to each calf on Days 3, 5, 7, 10, 12, 14, 17, 19 and 21. The calves were necropsied for nematode recovery on Days 75 or 76. There were no adverse reactions to treatment. Nematode counts and percentage reductions are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| | | Ivermectin (μg/kg/day) | | |
|---|---|---|---|---|
| **Nematode** | **Control** | **17** | **24** | **34** |
| *Cooperia oncophora* | 1778 | 100% | 100% | 100% |
| *Cooperia punctata* | 1372 | 100% | 100% | 100% |
| *Cooperia* spp, immature | 826 | 100% | 100% | 100% |
| *Nematodirus helvetianus*, immature | 437 | 100% | 100% | 100% |

Efficacy against the cattle tick, *A. americanum*, was also investigated. Twenty-five adult pairs of *A. americanum* were applied to each animal on Day 7. Detaching females were collected each day and incubated for oviposition. One hundred and twelve of 114 ticks collected from control animals produced viable eggs. None of 66 female ticks collected from calves treated at 24 μ/kg/day produced eggs and only one of 61 female ticks collected from calves treated at 34 μg/kg/day produced eggs.

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3. Study ASR 11170 was conducted in the United Kingdom to determine the dose level of ivermectin delivered intraruminally required to provide efficacy against established nematode infections. Fifteen calves were allocated by restricted randomization based on body weight to three treatment groups. Cattle in one group acted as untreated controls while cattle in the other two groups were given Alzet pumps delivering ivermectin at nominal dose levels of 10 or 40 μg/kg/day (calculated actual mean dose levels were 11 and 44 μg/kg/day). Treatments were administered on Day 0. Infective nematode larvae were administered to each calf 27 to 35 days before the osmotic pumps were given so that most parasites were expected to be adults at the time of treatment. The calves were necropsied for nematode recovery on Day 28. There were no adverse reactions to treatment. Nematode counts and percentage reductions are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| | | Ivermectin (μg/kg/day) | |
|---|---|---|---|
| **Nematode** | **Control** | **11** | **44** |
| *Ostertagia ostertagi* | 618 | >99% | 100% |
| *Cooperia oncophora* | 5126 | 96% | >99% |
| *Nematodirus helvetianus*, immature | 82 | 93% | 100% |
| *Dictyocaulus viviparus* | 84 | 100% | 100% |

Investigator: Dr. D. G. Baggott
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An ivermectin release rate of 12 mg/day was selected to ensure that animals at the top of the body weight range for the product receive an effective dose rate throughout the delivery period. Based on the results from ASR 13469, the dose levels of ivermectin required to provide 95% efficacy ($ED_{95}$) and 99% efficacy ($ED_{99}$) against the dose-limiting parasite species, *N. helvetianus*, are 13.3 and 28.8 μg/kg/day, respectively. The IVOMEC SR Bolus is recommended for use in cattle weighing 125 to 300 kg at the time of administration. A 300 kg animal could grow as much as 1 kg/day resulting in a body weight of approximately 435 kg at the end of the 135 day bolus delivery period. The release rate of 12 mg/day supplies 27.6 μg/kg/day of ivermectin to a 435 kg animal which will provide between 95% and 99% efficacy against *N. helvetianus*.

## B. Dose Confirmation

Two different types of bolus were used in the dose confirmation studies. A prototype bolus designated "3B" was used in some studies and a second prototype designated "5APT" was used in others. The 3B prototype delivered ivermectin at 8 or 12 mg/day for approximately 90 days. The 5APT prototype delivered ivermectin at 8 or 12 mg/day for 135 days. The commercial SR bolus is a 5APT device delivering ivermectin at 12 mg/day for 135 days.

### ENDOPARASITE DOSE CONFIRMATION

1. Study ASR 11772 was conducted in South Africa to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections present on the day of treatment. Twenty-four cattle weighing 160 to 210 kg and carrying induced nematode infections were allocated by restricted randomization on body weight within breed and sex to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 42-50 μg/kg/day) administered on Day 0. Cattle were necropsied by replicate on Days 28, 29 or 30 for nematode recovery. There were no adverse reactions to treatment. Nematode counts and percentage reduction are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Bunostomum phlebotomum* | 296 | 0 | 100% |

Investigator: Dr. M. D. Soll
Merck Research Laboratories
Hennops River
Republic of South Africa

2. Study ASR 11851 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections present on the day of treatment. Twelve cattle weighing 197 to 255 kg and carrying induced nematode infections were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 31-38 μg/kg/day) administered on Day 0. Cattle were necropsied by replicate on Days 28 or 29 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reductions are summarized below.

**Arithmetic mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Haemonchus placei* | 2192 | 0 | 100% |
| *Oesophagostomum radiatum* | 102 | 0 | 100% |
| *Dictyocaulus viviparus* | 37 | 0 | 100% |

Investigator: Dr. R. Alva-Valdes
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USA

3. Study ASR 11864 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections present on the day of treatment. Twelve cattle weighing 172 to 336 kg and carrying natural nematode infections were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were each given one placebo bolus. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 28-47 μg/kg/day). Treatments were administered on Day 0, and the animals were necropsied on Day 28 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reductions are summarized in the following table.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Ostertagia ostertagi* | 957 | 0 | 100% |
| *Trichostrongylus axei* | 315 | 0 | 100% |

Investigator: Dr. G. Zimmerman
Oregon State University
Corvallis, OR
USA

4. Study ASR 11936 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections present on the day of treatment. Twelve cattle weighing 154 to 182 kg and carrying induced nematode infections were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 44-52 μg/kg/day). Treatments were administered on Day 0, and the animals were necropsied on Days 28 or 29 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reduction are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Bunostomum phlebotomum* | 51 | 0 | 100% |

Investigator: Dr. T. A. Yazwinski
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USA

5. Study ASR 12308 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections present on the day of treatment. Twelve cattle weighing 136 to 228 kg and carrying natural nematode infections, including inhibited fourth-stage larvae ($IL_4$) of *Ostertagia* spp, were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were each given one placebo bolus. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 42-53 µg/kg/day). Treatments were administered on Day 0, and the animals were necropsied on Day 28 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reductions are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Ostertagia* spp[a], $IL_4$ | 342 | 0 | 100% |
| *Cooperia* spp[b] | 3130 | 3 | >99% |

[a] Includes *O. ostertagi* and *O. lyrata*
[b] Includes *C. oncophora, C. punctata* and *C. surnabada*

Investigator: Dr. G. Zimmerman
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6. Study ASR 12451 was conducted in Germany to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections present on the day of treatment. Twelve cattle weighing 152 to 193 kg and carrying induced nematode infections were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 5APT bolus delivering ivermectin at 8 mg/day (dose range 42-53 μg/kg/day). Treatments were administered on Day 0, and the animals were necropsied on Day 14 for nematode recovery.

   There were no adverse reactions to treatment during the study. Nematode counts and percentage reduction are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Nematodirus helvetianus* | 1769 | 0 | 100% |

Investigator: Dr. E. M. Heinze-Mutz
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Germany

7. Study ASR 12844 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections present on the day of treatment. Fourteen cattle weighing 145 to 180 kg and carrying induced nematode infections were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 5APT bolus delivering ivermectin at 8 mg/day (dose range 44-55 μg/kg/day). Treatments were administered on Day 0, and the animals were necropsied on Day 14 or 15 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reduction are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Haemonchus placei* | 174 | 0 | 100% |
| *Ostertagia ostertagi* | 4014 | 0 | 100% |
| *Trichostrongylus axei* | 1087 | 0 | 100% |
| *Trichostrongylus colubriformis* | 366 | 0 | 100% |
| *Cooperia* spp[a] | 4443 | 0 | 100% |
| *Nematodirus helvetianus* | 360 | 0 | 100% |
| *Oesophagostomum radiatum* | 109 | 0 | 100% |
| *Dictyocaulus viviparus* | 61 | 0 | 100% |

[a] Includes *C. oncophora*, *C. punctata*, and *C. surnabada*

Investigator: Dr. R. Alva-Valdes
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USA

8. Study ASR 11581 was conducted in the United Kingdom to confirm the prophylactic efficacy of the IVOMEC SR Bolus against newly acquired infective nematode larvae. Ten cattle with no known prior exposure to nematode infections and weighing 165 to 182 kg were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 44-49 μg/kg/day). Treatments were administered on Day 0, and each animal was challenged with infective nematode larvae on Days 28 and 42. The cattle were necropsied on Day 63 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reductions are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Nematodirus helvetianus* | 2604 | 0 | 100% |
| *Dictyocaulus viviparus* | 150 | <1 | >99% |

Investigator: Dr. D. G. Baggott
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9. Study ASR 11773 was conducted in South Africa to confirm the prophylactic efficacy of the IVOMEC SR Bolus against newly acquired infective nematode larvae. Twenty-four cattle with no known prior exposure to nematode infections and weighing 150 to 205 kg were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 39-53 μg/kg/day). Treatments were administered on Day 0, and each animal was challenged with infective nematode larvae on Days 27 and 28 after treatment. The cattle were necropsied on Days 70, 71 or 72 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reduction are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Bunostomum phlebotomum* | 346 | 0 | 100% |

Investigator: Dr. M. D. Soll
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10. Study ASR 11854 was conducted in the USA to confirm the prophylactic efficacy of the IVOMEC SR Bolus against newly acquired infective nematode larvae. Twelve cattle with no known prior exposure to nematode infections and weighing 166 to 249 kg were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 32-48 μg/kg/day). Treatments were administered on Day 0, and each animal was challenged with infective larvae on Days 28 and 42 after treatment. The cattle were necropsied on Days 77 or 78 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reductions are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Haemonchus placei* | 1037 | 0 | 100% |
| *Cooperia* spp[a] | 5428 | 0 | 100% |
| *Nematodirus helvetianus* | 67 | 0 | 100% |
| *Dictyocaulus viviparus* | 35 | 0 | 100% |

[a] Includes *C. oncophora*, *C. punctata* and *C. surnabada*

Investigator: Dr. R. Alva-Valdes
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Fulton, MO
USA

11. Study ASR 11937 was conducted in the USA to confirm the prophylactic efficacy of the IVOMEC SR Bolus against newly acquired infective nematode larvae. Twelve cattle weighing 166 to 177 kg were allocated by restricted randomization based on body weight and sex to two treatment groups. The cattle had been treated with fenbendazole on Day -4 to ensure that they were not carrying nematode infections. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 47-48 μg/kg/day). Boluses were administered on Day 0, and each animal was challenged with infective larvae on Days 28 and 42 after treatment. The cattle were necropsied on Days 77 or 78 for nematode recovery. There were no adverse reactions to treatment during the study. Nematode counts and percentage reductions are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Haemonchus placei* | 1079 | 0 | 100% |
| *Trichostrongylus axei* | 2002 | <1 | >99% |
| *Oesophagostomum radiatum* | 719 | 0 | 100% |

Investigator: Dr. T. A. Yazwinski
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USA

12. Study ASR 13989 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against endoparasite infections including *O. ostertagi* inhibited $L_4$ present at the time of treatment and against newly acquired infective nematode larvae. Sixteen cattle weighing 145 to 215 kg were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one commercial bolus delivering ivermectin at 12 mg/day (dose range 50-85 µg/kg/day). The animals were carrying natural nematode infections at the time of treatment on Day 0 and continued to graze on contaminated pasture until Day 135. Each animal was also inoculated with infective nematode larvae on Days 0, 1, 35, 70, 105 and 120 after treatment. On Day 135 all cattle were moved to a pen with a concrete floor where they remained until necropsy on Days 21 or 22 for nematode recovery. There were no adverse reactions to treatment. Nematode counts and percentage reduction are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Ostertagia ostertagi* | 20693 | 80 | >99% |
| *Ostertagia ostertagi* ($IL_4$) | 2303 | 0 | 100% |
| *Trichostrongylus axei* | 15588 | 21 | >99% |
| *Trichostrongylus colubriformis* | 705 | 3 | >99% |
| *Cooperia* spp[a] | 7675 | 159 | 98% |
| *Bunostomum phlebotomum* | 18 | 0 | 100% |
| *Oesophagostomum radiatum* | 230 | 0 | 100% |

[a] Includes *C. oncophora* and *C. punctata*

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13. Study ASR 15064 was conducted in the USA to confirm the prophylactic efficacy of the IVOMEC SR Bolus against newly acquired infective nematode larvae. Twenty-two cattle with no known prior exposure to nematode infections and weighing 107 to 148 kg were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one commercial bolus delivering ivermectin at 12 mg/day (dose range 87-121 μg/kg/day). Treatments were administered on Day 0, and each animal was challenged with infective nematode larvae on Day 28. The cattle were necropsied on Day 49 for nematode recovery. There were no adverse reactions to treatment. Nematode counts and percentage reduction are summarized below.

**Arithmetic Mean Nematode Counts and Percentage Reduction**

| Nematode | Control | SR Bolus | % Reduction |
|---|---|---|---|
| *Nematodirus helvetianus* | 336 | <1 | >99% |

Investigator: Dr. J. E. Holste
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## ECTOPARASITE DOSE CONFIRMATION

1. Study ASR 11662 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against *Hypoderma* spp larvae. Eighteen cattle weighing 188 to 208 kg were allocated by restricted randomization based on body weight to three treatment groups. Cattle in one group were each given one placebo bolus on Day 0. Cattle in the second and third groups were each given one prototype 3B bolus delivering ivermectin at 12 mg/day (dose range 58-64 μg/kg/day) on Day 0 (24 April) or Day 57 (20 June), respectively. The animals grazed together on pasture throughout the study and were expected to be exposed to *Hypoderma* spp flies during spring and summer (approximately April to September). Each animal was observed weekly for *Hypoderma* spp lesions in late fall and winter (November to February). There were no adverse reactions to treatment. *Hypoderma* spp lesion counts and percentage reductions are summarized below.

**Arithmetic Mean *Hypoderma* spp Lesion Counts and Percentage Reduction**

| Treatment Group | Mean Count | % Reduction |
|---|---|---|
| Control | 5.2 | - |
| SR Bolus - April | 0 | 100% |
| SR Bolus - June | 0 | 100% |

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Stillwater, OK
USA

2. Study ASR 11853 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against *Hypoderma* spp larvae. Eighteen cattle weighing 98 to 184 kg were allocated by restricted randomization based on body weight and sex to three treatment groups. Cattle in one group were each given one placebo bolus on Day 0. Cattle in the second and third groups were each given one prototype 3B bolus on Day 0 (18 April) or Day 60 (17 June), respectively. Animals weighing less than 135 kg received a bolus delivering 8 mg of ivermectin/day; animals weighing greater than 135 kg received a bolus delivering 12 mg of ivermectin/day (dose range 61-86 mg/kg/day). The animals grazed together on one or two pastures throughout the study and were expected to be exposed to *Hypoderma* spp flies during spring and summer (approximately April to September). Each animal was observed approximately weekly for *Hypoderma* spp lesions in winter and early spring (January to early April). There were no adverse reactions to treatment. *Hypoderma* spp lesion counts and percentage reduction are summarized below.

**Arithmetic Mean *Hypoderma* spp Lesion Counts and Percentage Reduction**

| Treatment Group | Mean Count | % Reduction |
|---|---|---|
| Control | 6.8 | - |
| SR Bolus - April | 0 | 100% |
| SR Bolus - June | 0 | 100% |

Investigator: Dr. J. E. Holste
Merck Research Laboratories
Fulton, MO
USA

3. Study ASR 12096 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against *Psoroptes ovis* mites. Twelve cattle weighing 207 to 249 kg with induced *P. ovis* infestations were allocated by restricted randomization based on mite counts to two treatment groups. Cattle in one group were left untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 32-35 µg/kg/day). Treatments were administered on Day 0, and mites were counted in skin scrapings taken at weekly intervals from Day -1 to Day 55. There were no adverse reactions to treatment. Mite counts and percentage reduction are summarized below.

**Arithmetic Mean *Psoroptes ovis* Mite Counts and Percentage Reduction**

| **Count Day** | **-1** | **6** | **13** | **20** | **27** | **34** | **41** | **48** | **55** |
|---|---|---|---|---|---|---|---|---|---|
| Controls | 58 | 182 | 157 | 1178 | 2591 | 1446 | 1066 | 914 | 576 |
| SR Bolus | 70 | 239 | 1 | <1 | 0 | <1 | 0 | 0 | 0 |
| % Reduction | - | - | >99% | >99% | 100% | >99% | 100% | 100% | 100% |

Investigator: Dr. H. G. Kinzer
New Mexico State University
Las Cruces, NM
USA

4. Study ASR 14111 was conducted in Germany to confirm the efficacy of the IVOMEC SR Bolus against *Psoroptes ovis* mites. Eighteen cattle weighing 340 to 436 kg were allocated by restricted randomization based on body weights to three treatment groups. Cattle in Groups 1 and 3 were untreated while cattle in Group 2 were each given one commercial bolus delivering ivermectin at 12 mg/day (dose range 30-33 μg/kg/day). Treatments were administered on Day 0. Animals in Groups 1 and 2 were carrying induced *P. ovis* infestations at the time of treatment. Animals in Groups 2 and 3 were challenged with *P. ovis* mites on Day 55. Mites were counted at approximately weekly intervals from Day -2 to Day 55 in Groups 1 and 2 and on Days 77 and 84 in Groups 2 and 3. There were no adverse reactions to treatment. Mite counts and percentage reduction are summarized below.

**Arithmetic Mean *Psoroptes ovis* Mite Counts and Percentage Reduction**

| **Count Day** | **-2** | **7** | **14** | **21** | **28** | **34** | **42** | **49** | **55** | **77** | **84** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Control (Group 1) | 236 | 396 | 439 | 392 | 288 | 308 | 276 | 290 | 255 | - | - |
| Control (Group 3) | - | - | - | - | - | - | - | - | - | 377 | 537 |
| SR Bolus | 215 | 205 | 126 | 21 | 2 | <1 | <1 | 0 | 0 | 0 | 0 |
| % Reduction | - | 48% | 71% | 95% | >99% | >99% | >99% | 100% | 100% | 100% | 100% |

Investigator: Dr. S. Rehbein
Merck Research Laboratories
Kathrinenhof, Lauterbach
Germany

5. Study ASR 11549 was conducted in Germany to confirm the efficacy of the IVOMEC SR Bolus against *Sarcoptes scabiei* mites. Ten cattle weighing 194 to 302 kg with induced *S. scabiei* infestations were used. Replicates were formed of two animals of the same breed and sex with similar body weights and mite counts. Within replicates one animal was randomly allocated to each of two groups. Cattle in one group were each given one placebo bolus. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (animals weighing approximately 200 kg) or 12 mg/day (animals weighing approximately 300 kg), (dose range 40-42 μg/kg/day). Treatments were administered on Day 0, and mites were counted in skin scrapings taken at weekly intervals from Day 0 (pretreatment) to Day 56. There were no adverse reactions to treatment. Mite counts and percentage reduction are summarized below.

**Arithmetic Mean *Sarcoptes scabiei* Mite Counts and Percentage Reduction**

| **Count Day** | **0** | **7** | **14** | **21** | **28** | **35** | **42** | **49** | **56** |
|---|---|---|---|---|---|---|---|---|---|
| Controls | 159 | 113 | 140 | 141 | 159 | 158 | 132 | 133 | 134 |
| SR Bolus | 125 | <1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Reduction | - | >99% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |

Investigator: Dr. E. M. Heinze-Mutz
Merck Research Laboratories
Kathrinenhof, Lauterbach
Germany

6. Study ASR 12036 was conducted in Germany to confirm the efficacy of the IVOMEC SR Bolus against *Sarcoptes scabiei* mites. Twelve cattle weighing 181 to 215 kg with induced *S. scabiei* infestations were allocated by restricted randomization based on mite counts to two treatment groups. Cattle in one group were each given one placebo bolus. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 37-44 μg/kg/day). Treatments were administered on Day 0, and mites were counted in skin scrapings taken at weekly intervals from Day 0 to Day 56. There were no adverse reactions to treatment. Mite counts and percentage reduction are summarized below.

**Arithmetic Mean *Sarcoptes scabiei* Mite Counts and Percentage Reduction**

| Count Day | 0 | 7 | 14 | 21 | 28 | 35 | 42 | 49 | 56 |
|---|---|---|---|---|---|---|---|---|---|
| Control | 138 | 139 | 176 | 149 | 153 | 183 | 149 | 202 | 206 |
| SR Bolus | 124 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Reduction | - | 96% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |

Investigator: Dr. E. M. Heinze-Mutz
Merck Research Laboratories
Kathrinenhof, Lauterbach
Germany

7. Study ASR 12066 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against the sucking louse, *Linognathus vituli*. Twelve cattle weighing 200 to 340 kg with natural *L. vituli* infestations were allocated by restricted randomization based on lice counts to two treatment groups. Cattle in one group were untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 12 mg/day (dose range 48-54 µg/kg/day). Treatments were administered on Day 0, and lice were counted at weekly intervals from Day -1/0 to Day 56. There were no adverse reactions to treatment. Lice counts and percentage reduction are summarized below.

**Arithmetic Mean *Linognathus vituli* Counts and Percentage Reduction**

| **Count Day** | **-1/0** | **7** | **14** | **21** | **28** | **35** | **42** | **49** | **56** |
|---|---|---|---|---|---|---|---|---|---|
| Controls | 40 | 75 | 34 | 49 | 37 | 31 | 12 | 3 | 4 |
| SR Bolus | 74 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Reduction | - | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |

Investigator: Dr. J. E. Holste
Merck Research Laboratories
Fulton, MO
USA

8. Study ASR 12070 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against the sucking lice, *Linognathus vituli* and *Solenopotes capillatus*. Twelve cattle weighing 146 to 195 kg with natural lice infestations were allocated by restricted randomization based on *S. capillatus* counts to two treatment groups. Cattle in one group were untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 42-55 µg/kg/day). Treatments were administered on Day 0, and lice were counted at weekly intervals from Day 0 to Day 56. There were no adverse reactions to treatment. Lice counts and percentage reduction are summarized below.

**Arithmetic Mean Lice Counts and Percentage Reduction**

| **Count Day** | **0** | **7** | **14** | **21** | **28** | **35** | **42** | **49** | **56** |
|---|---|---|---|---|---|---|---|---|---|
| *Linognathus vituli* | | | | | | | | | |
| Control | 149 | 94 | 96 | 74 | 65 | 41 | 44 | 30 | 30 |
| SR Bolus | 197 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Reduction | - | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| *Solenopotes capillatus* | | | | | | | | | |
| Control | 147 | 141 | 137 | 82 | 57 | 42 | 32 | 29 | 30 |
| SR Bolus | 73 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Reduction | - | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |

Investigator: Dr. J. E. Lloyd
University of Wyoming
Laramie, WY
USA

9. Study ASR 12094 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against the sucking louse, *Solenopotes capillatus*. Twelve cattle weighing 194 to 250 kg with natural *S. capillatus* infestations were allocated by restricted randomization based on lice counts within sex to two treatment groups. Cattle in one group were untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 12 mg/day (dose range 48-60 μg/kg/day). Treatments were administered on Day 0, and lice were counted at weekly intervals from Day 0 to Day 56. There were no adverse reactions to treatment. Lice counts and percentage reduction are summarized below.

**Arithmetic Mean *Solenopotes capillatus* Counts and Percentage Reduction**

| Count Day | 0 | 7 | 14 | 21 | 28 | 35 | 42 | 49 | 56 |
|---|---|---|---|---|---|---|---|---|---|
| Control | 841 | 902 | 889 | 873 | 809 | 713 | 627 | 537 | 414 |
| SR Bolus | 843 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Reduction | - | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |

Investigator: Dr. J. A. Hair
Oklahoma State University
Stillwater, OK
USA

10. Study ASR 11659 was conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus against *Amblyomma americanum*. Twelve cattle weighing 170 to 216 kg were allocated by restricted randomization based on body weight to two treatment groups. Cattle in one group were untreated. Cattle in the second group were each given one prototype 3B bolus delivering ivermectin at 8 mg/day (dose range 39-46 μg/kg/day). Treatments were administered on Day 0, and unengorged female ticks were applied to each animal on Days 28 and 35. Under normal conditions, female ticks engorge blood and then detach from the animal. Detaching partial or fully engorged ticks were collected and counted each day. The results demonstrated that ticks on control animals completed engorgement while those on the SR Bolus-treated animals failed to engorge. There were no adverse reactions to treatment. Tick counts and percentage reduction are summarized below.

**Total Detaching *Amblyomma americanum* Females and**

**Percentage Reduction**

| Treatment | Tick Count | % Red |
|---|---|---|
| Control | 226 | - |
| SR Bolus | 12 | 95% |

Investigator: Dr. J. Lancaster
University of Arkansas
Fayetteville, AR
USA

11. Study ASR 13469 was conducted in the USA and was determine to be acceptable as dose confirmation for the cattle tick, *Amblyomma americanum*. Efficacy against the cattle tick was investigated in control calves and calves treated at the highest ivermectin dose level (40 μg/kg/day). Twenty-five adult pairs of *A. americanum* were applied to each animal on Day 10. Detaching females were collected each day and incubated for oviposition. Based on mean weight of eggs produced, ivermectin at 40 μg/kg/day provided 100% control of *A. americanum*.

    Investigator: Dr. J. R. Egerton
    Merck Research Laboratories
    Rahway, NJ
    USA

## 5. Field Studies

Three field studies were conducted in the USA to confirm the efficacy of the IVOMEC SR Bolus under field conditions. In each study replicates of five cattle were formed based on body weight or order of presentation. Within replicates one animal was randomly allocated to an untreated control group, and the other four each received one commercial SR bolus delivering ivermectin at 12 mg/day (dose range 42-88 μg/kg/day). The cattle weighed 137 to 286 kg at the beginning of the studies. There were 75 control animals and 300 bolus-treated animals.

Treatments were administered on Day 0 and fecal samples were collected for nematode egg counts before treatment and on Days 35, 70, 105, 119/120 and 134/136. Blood samples were collected for plasma ivermectin assays on the same days. There were no adverse reactions to treatment. Trial sites, investigators, fecal egg count and plasma ivermectin assay results are shown below.

| **Study Number** | **Site** | **Investigator** |
|---|---|---|
| ASR 13990 | Fayetteville, Arkansas | Dr. T. A. Yazwinski<br>University of Arkansas<br>Fayetteville, AR<br>USA |
| ASR 14003 | Gainesville, Florida | Dr. C. H. Courtney<br>University of Florida<br>Gainesville, FL<br>USA |
| ASR 14006 | Watkinsville, Georgia | Dr. J. A. Stuedemann<br>USDA<br>Watkinsville, GA<br>USA |

**Arithmetic Mean Fecal Nematode Egg Counts and Percentage Reduction**

| **Count Day** | **(-)2 (-)0** | **35** | **70** | **105** | **119/120** | **134/136** |
|---|---|---|---|---|---|---|
| ASR 13990 | | | | | | |
| Control | 97 | 70 | 25 | 14 | 43 | 61 |
| SR Bolus | 76 | <1 | <1 | <1 | <1 | <1 |
| % Reduction | - | >99% | >99% | >99% | >99% | >99% |
| ASR 14003 | | | | | | |
| Control | 363 | 177 | 78 | 47 | 67 | 68 |
| SR Bolus | 455 | 2 | <1 | 0 | <1 | <1 |
| % Reduction | - | 99% | >99% | 100% | >99% | >99% |

| ASR 14006 | | | | | | |
|---|---|---|---|---|---|---|
| **Count Day** | **(-)2 (-)0** | **35** | **70** | **105** | **119/120** | **134/136** |
| Control | 502 | 389 | 425 | 280 | 143 | 206 |
| SR Bolus | 411 | 1 | 0 | 0 | 0 | 0 |
| % Reduction | - | >99% | 100% | 100% | 100% | 100% |

**Arithmetic Mean Plasma Ivermectin Levels**
**(5APT Bolus, ng/mL Ivermectin $B_{1a}$)**

| **Trial Day** | **0** | **35** | **70** | **105** | **119/120** | **134/136** |
|---|---|---|---|---|---|---|
| ASR 13990 | 0.01 | 7.50 | 4.93 | 5.03 | 4.38 | 1.82 |
| ASR 14003 | 0 | 6.02 | 4.61 | 4.09 | 4.54 | 1.47 |
| ASR 14006 | 0 | 5.51 | 4.25 | 4.62 | 5.46 | 1.85 |

**Effectiveness Conclusions**

It was concluded that IVOMEC® (ivermectin) SR Bolus is an effective broad spectrum antiparasitic compound that will treat established gastrointestinal and lung nematodes and will prevent the establishment of new infections for approximately 135 days. The treatment will control established mange mite and sucking lice infestations. The administration of the bolus will control migrating grubs and will provide protection for the duration of the bolus activity. In addition, in female ticks the SR bolus will interfere with the engorgement of blood and the completion of the life cycle.

## 5. Target Animal Safety (TAS)

Study ASR 12848 was conducted in the USA to determine the safety of ivermectin delivered by SR bolus at 1, 3 or 5X the recommended dose level of 40 μg/kg/day. Twelve castrated male and 12 female calves weighing 142 to 200 kg were allocated by restricted randomization based on body weight within sex to four treatment groups. Cattle in one group were left untreated. Cattle in the other groups received one or more prototype 5APT boluses so that the dose level of ivermectin delivered was 1X, 3X or 5X.

Treatments were administered on Day 0. Body weights, feed consumption and clinical health were monitored from Day -7 to Day 133 or 136. Blood was collected on six occasions for clinicopathological evaluation, and the calves were necropsied on Day 136 or 137 for gross and histopathological examination. Mild digestive disturbances were observed in some calves that received three or more boluses. Calves in the groups treated at 3X and 5X dose also gained less weight to Day 112 (3X and 5X groups) and Day 136 (5X group), than controls. These effects were attributed to the physical mass of the devices rather than to the ivermectin. Mild symmetrical mydriasis was observed in four of six calves treated at 3X dose and two of six calves treated at 5X dose. One calf treated at 3X showed mild depression. The mydriasis and depression may have been due to ivermectin toxicity. No other adverse reactions were observed during the study.

Investigator:
Dr. D. H. Wallace
Merck Research Laboratories
Fulton, MO
USA

**TAS Conclusions**

The study demonstrated that IVOMEC® Bolus is safe when administered to cattle under the labeled conditions of use.

## 6. Human Food Safety

### a. Drugs for use in food animals

#### 1. Toxicity tests

For a complete summary of the toxicity tests for ivermectin, please consult the FOI Summary for NADA 128-409, IVOMEC® (ivermectin) 1% Injection for Cattle.

#### 2. Safe concentrations and tolerance

As discussed in the FOI Summary for NADA 128-409, IVOMEC® (ivermectin) Injection for Cattle, the following safe concentrations in edible tissues have been calculated from the no-observed-effect-level in the most sensitive study in the most sensitive species:

| Tissue | Safe Concentration (ppb) |
|---|---|
| Muscle | 120 |
| Liver | 240 |
| Kidney | 360 |
| Fat | 480 |

Also under NADA 128-409, a tolerance of 100 ppb was established for the marker residue (ivermectin B1a) in cattle liver.

#### 3. Metabolism and total residue depletion

Total radioactive residues in edible tissues of cattle dosed orally (intraruminally) with tritiated ivermectin radiolabeled at the C-22 and C-23 position were determined in a residue and metabolism study, RN 189, conducted in support of the oral paste (NADA 137-006) formulation of ivermectin for cattle. This study confirmed that the target tissue (liver), marker substance ($H_2B_{1a}$) and tolerance (100 ppb) established for ivermectin with the IVOMEC 1% Injection (NADA 128-409) are valid assignments for ivermectin dosed intraruminally. For a complete summary of the residue and metabolism of ivermectin given orally, please consult the FOI Summary for NADA 137-006.

To assure that sustained release of ivermectin for ~135 days does not result in enzyme induction and altered ivermectin metabolism, an additional radiometabolism study (CA 273) was conducted. Three steers were dosed with ivermectin (80% component $H_2B_{1a}$, 20% component $H_2B_{1b}$) *via* an ivermectin bolus designed to deliver the drug for 135 days at ~12 mg/day. A single intraruminal pulse dose of 200 mg/kg of $[^3H]H_2B_{1a}$ was given to each of the bolus-treated steers, and to each of three control (no bolus) steers, on day 90 following bolus administration.

Plasma and liver samples were collected 7 days after dosing with $[^3H]$ $H_2B_{1a}$. The total radioactive residue in plasma and liver is shown below. The nanogram equivalents of total radioactive residue per mL of plasma and gram of liver (ppb) at necropsy were not different between treatment groups. Liver $H_2B_{1a}$ residue concentrations were calculated to be 59 and 56 ppb, based on total residue and reversed-phase HPLC, thus accounting for slightly more than one-half (52 and 58%) of the total liver residue in bolus-treated and control steers, respectively. These results demonstrate that the plasma and liver total residues are comparable for both sets of animals, as are the levels of unmetabolized parent drug in liver.

Nanogram Equivalents Per Gram (mL) of Total Radioactive Residue and $H_2B_{1a}$

| **Administration of Drug** | **Liver** | **Plasma** |
|---|---|---|
| | **ppb**[a] | |
| Bolus + $[^3H]H_2B_{1a}$ | 114 (59)[b] | 5.7 |
| $[^3H]H_2B_{1a}$ | 96 (56)[b] | 5.0 |

[a]Values are the average for three steers
[b]$H_2B_{1a}$ ppb in parentheses

Nearly all of the radioactivity in liver from bolus-treated and control animals was found to be solvent extractable, and reversed-phase HPLC profiling of the extracted radioactivity gave the results shown below.

**HPLC Profiles**
**% of Total Liver Residue Radioactivity**

| Administration of Drug | $H_2B_{1a}$ | 24-$HOCH_2$ | $3^2$-O-desmethyl |
|---|---|---|---|
| Bolus + [$^3$H]$H_2B_{1a}$ | 52 | 39 | 4.7 |
| [$^3$H]$H_2B_{1a}$ only | 58 | 32 | 6.9 |

The HPLC profiles were similar between groups with most of the non-$H_2B_{1a}$ radioactivity from livers of bolus-treated and control steers eluting at the retention time of 24-hydroxymethyl $H_2B_{1a}$ (24-$HOCH_2$); ~5% of the radioactivity eluted at the retention time of $3^2$-O-desmethyl $H_2B_{1a}$. Profiling using normal-phase HPLC gave similar results. These *in vivo* results support the conclusion that there is no significant induction or inhibition of hepatic ivermectin-metabolizing enzymes due to bolus administration.

The same conclusion can be drawn from *in vitro* incubations using [$^3$H]$H_2B_{1a}$ and microsomes prepared from livers of control steers (no bolus), from steers given a bolus and from steers given a bolus and pulsed with [$^3$H]$H_2B_{1a}$. For purposes of this summary, results from the latter two groups were combined. Reversed-phase HPLC profiling results are presented below.

**HPLC Profiles**
**% of Total Radioactivity**

| **Treatment Group** | **$H_2B_{1a}$** | **24-$HOCH_2$** | **$3^2$-O-desmethyl** |
|---|---|---|---|
| Bolus only and Bolus + [$^3$H]$H_2B_{1a}$ | 89 | 4.8 | 4.3 |
| Control | 89 | 3.2 | 5.7 |

Both metabolites account for small percentages of the total radioactivity, with the substrate accounting for ~90% (similar results were obtained using normal-phase HPLC).

Examination by reversed-phase HPLC of solvent-extractable radioactivity in the livers of steers dosed subcutaneously with [$^3$H]ivermectin demonstrated that unaltered drug was the major liver residue component, and that 24-hydroxymethylation was the main metabolic pathway. Thus the liver

metabolism of $H_2B_{1a}$ (and hence ivermectin) in steers appears to be independent of the route of administration. Although nearly all the radioactivity in liver from bolus-treated and control (no bolus) animals was found to be solvent extractable, it is possible that even a small amount of bound residue may accumulate when a continuous dosing scheme (e.g., sustained-release intraruminal bolus) is employed. After exhaustive extraction of liver tissue from the steers receiving a pulse dose of $[^3H]H_2B_{1a}$, the nonextractable residue represented approximately 0.25% of the total radioactive residue at day 7 post pulse $[^3H]H_2B_{1a}$ dose.

There was no significant difference between the percent of nonextractable residue between control (no bolus) and bolus-treated steers. The maximum amount of bound residue, according to a pharmacokinetic model, would be less than 3 ppb. At the end of the assigned withdrawal time (180 days after bolus administration), the bound residue levels would be less than 0.5 ppb -- approximately 1% of the allowable level of ivermectin-related residues. Thus, the contribution of the bound residue to the total residue is negligible, and the bound residue does not adversely affect the marker proportion of the total residue. This finding, together with the HPLC metabolite profiles described earlier, confirms that 100 ppb is a valid tolerance for the sustained release oral dosing scheme afforded by the IVOMEC SR Bolus.

Comparative metabolism studies conducted for NADAs 128-409 and 137-006 indicate that the metabolism of $[^3H]H_2B_{1a}$ in steers and rats (the toxicity test species; oral dosing) is similar. Unaltered drug is the major liver residue component in both species. The HPLC profiles of the radioactive residue in the liver are highly comparable with respect to the metabolite components. The major metabolic route in steer and rat liver is hydroxylation of the 24-methyl group. $3^2$-O-Desmethyl metabolites are observed in steer liver, and the presence of these metabolites in rat liver is suggested by the appearance of small radioactive peaks with HPLC retention times identical to those of the $3^2$-O-Desmethyl compounds. $3^2$-O-Desmethyl metabolites have also been identified in *vitro* incubations of $[^3H]H_2B_{1a}$ with rat liver and steer liver microsome. Thus, the test species is exposed to the major drug residue components known to be formed in the steer.

**4. Studies demonstrating a withdrawal time**

A tissue residue depletion study was performed to determine the marker residue (component $H_2B_{1a}$) concentration in bovine tissues resulting from the administration of the bolus to steers and heifers. Animals were sacrificed at 117, 147, 152, 157, 162, 172, 182 and 192 days post-administration, and tissues were collected from each treated animal. Another five animals served as unmedicated controls and were sacrificed on day 168.

Marker residue assays were conducted on bovine livers (the target tissue) for selected post-administration times using the high pressure liquid chromatography-fluorescence determinative method. The average marker residue concentrations found were as follows:

| **Days post-administration** | **117** | **147** | **152** | **157** | **162** | **172** | **Control** |
|---|---|---|---|---|---|---|---|
| **ppb** | 88 | 17 | 6 | 2 | 3 | 0 | 0 |
| **(No. of Animals)** | (n=5) | (n=8) | (n=8) | (n=8) | (n=8) | (n=5) | (n=5) |
| **Standard Deviation** | 30 | 19 | 4 | 1 | 3 | 0 | 0 |

Statistical analysis of the depletion data, using the upper tolerance limit containing 99 percentile of the population with 95% confidence, yields a withdrawal period of 145 days. That value was calculated using the current 100 ppb tolerance for ivermectin. The calculated withdrawal time was extended to 180 days (six-months) for labeling purposes as a practical and easy to remember withdrawal period for this product.

## 5. Regulatory methods

### a) Ivermectin Determinative Assay Scheme

The determinative assay measures the marker residue, $H_2B_{1a}$, by high pressure liquid chromatography (HPLC) of a fluorescent derivative. The marker residue is extracted into isooctane from an aqueous acetone homogenate of liver tissue. The isooctane is removed by evaporation and the extract purified by a series of acetonitrile-hexane-water partitions. The fluorescent derivative is formed by heating the isolate with an acetic anhydride + methylimidazole reagent. A chloroform solution of the derivative is purified over a silica column and concentrated by evaporation; reversed-phase HPLC is performed using methanol/water and fluorescence detection.

Quantitation is obtained by using a standard curve for the marker residue carried through the derivatization and subsequent steps. Recoveries from liver averaged 84% with a lower limit of reliable measurement of approximately 3 ppb.

b) **Ivermectin Confirmatory Assay Scheme**

The sample preparation and purification steps of the confirmatory assay are essentially the same as the determinative assay. The specificity is obtained by the production of two new species just prior to derivatization. The new species are produced by removing one of the saccharide groups with 1% sulfuric acid in isopropanol to form the monosaccharide or removing both saccharide groups with 1% sulfuric acid in methanol to form the aglycone $H_2B_{1a}$. Since these two treatments are so similar, the formation of the two new species and their chromatographic properties are unique and hence confirm the presence of the marker residue. In the confirmatory test, the liver extract is split into three parts. One part is used for each of the sulfuric acid treatments. These samples are separated from sulfuric acid by extractions and the fluorescent derivatives of the two new compounds are made. The third aliquot is derivatized without pretreatment. All three derivatives are then extracted into hexane with a small amount of isobutyl alcohol present. The HPLC determination is made as in the determinative assay. Three separate peaks are observed at three separate retention times which are compared with standards run through the procedure from the sulfuric acid addition step onward. Presence of and quantitation of the three peaks is confirmation that ivermectin is present.

c) **Validation**

The determinative and confirmatory methods were validated satisfactorily by FDA and USDA laboratories utilizing bovine and ovine tissue. The validated regulatory analytical methods for detection of residues of ivermectin are filed in the Food Additives Manual on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857).

## 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 IVOMEC® SR Bolus for Cattle is safe and effective for the treatment of established infections and prophylaxis against reinfection for approximately 135 days of gastrointestinal and pulmonary nematodes. The IVOMEC® SR bolus also treats established infestations and provides prophylaxis against cattle grubs (*Hypoderma* spp.), and controls sucking lice (*L. vituli*, *S. capillatus*) mange mites (*P. ovis*, *S. scabiei*) and ticks (*A. americanum*).

Residue and metabolism studies conducted for this NADA confirm that the current 100 ppb tolerance for ivermectin B1a (the marker residue) in cattle liver (the target tissue) is a valid tolerance when ivermectin is administered to cattle with the continuous oral dosing scheme afforded by the IVOMEC® SR Bolus. The withdrawal time following bolus administration is assigned at 180 days. A withdrawal interval of 145 days was calculated from a residue depletion study conducted with the bolus in steers and heifers, and that value was extended to 180 days (six-months) as a practical and easy to remember withdrawal period for the product.

The data submitted for IVOMEC® SR Bolus for cattle support the marketing of the product as an over-the-counter new animal drug. Adequate directions for use have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine (CVM) has concluded that this product shall have over-the-counter marketing status.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding contained in an environmental assessment may be seen in the Dockets Management Branch (HFV-305), Park Building (Room 1-23), 12420 Parklawn Dr., Rockville, Maryland 20855.

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act
this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, studies of animal safety, or in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for approval of the application and conducted or sponsored by the applicant.

IVOMEC® SR Bolus for cattle is under U.S. patent numbers:

| No. | Expiration Date |
|---|---|
| 5,122,128 | June 16, 2009 |
| 5,206,024 | April 27, 2010 |
| 5,213,809 | May 25, 2010 |
| 5,215,753 | June 1, 2010 |
| 5,223,266 | June 29, 2010 |
| 5,368,863 | June 29, 2010 |
| 5,372,776 | December 13, 2001 |
| 5,474,785 | July 20, 2010 |

ATTACHMENTS:

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855