Date of Approval Letter: November 24, 2003

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-841

IVOMEC (Ivermectin) Pour-On for Cattle

To add persistent effect periods for 3 additional parasite species and extend the period of persistent effect for 3 existing parasite species.

Sponsored by:
Merial Ltd.

1. GENERAL INFORMATION

A. File Number:	NADA 140-841
B. Sponsor:	Merial Ltd. 3239 Satellite Blvd., Bldg. 500 Duluth, GA 30096-4640 Drug Labeler Code: 050604
C. Established Name:	Ivermectin
D. Proprietary Name:	IVOMEC (ivermectin) Pour-On for Cattle
E. Dosage Form:	Topical solution
F. How Supplied:	250-mL, 1-liter, 2.5-liter, 5-liter, and 20-liter containers
G. How Dispensed:	Over-the-Counter (OTC)
H. Amount of Active Ingredients:	5 mg ivermectin/mL
I. Route of Administration:	Topical application along the topline extending from the withers to the tailhead
J. Species/Class:	Cattle
K. Recommended Dosage:	1 mL for each 22 pound body weight to provide 500 mcg ivermectin/kg body weight
L. Pharmacological Category:	Antiparasitic

M. Indications: For the effective treatment and control of these parasites.

Gastrointestinal Roundworms

Ostertagia ostertagi (including inhibited stage)	(adults and L_4)
Haemonchus placei	(adults and L_4)
Trichostrongylus axei	(adults and L_4)
T. colubriformis	(adults and L_4)
Cooperia oncophora	(adults and L_4)
Cooperia punctata	(adults and L_4)
Cooperia surnabada	(adults and L_4)
Strongyloides papillosus	(adults)
Oesophagostomum radiatum	(adults and L_4)
Trichuris spp.	(adults)

Lungworms
Dictyocaulus viviparus (adults and L_4)
Cattle Grubs (parasitic stages)
Hypoderma bovis
H. lineatum
Mites
Sarcoptes scabiei var. *bovis*
Lice
Linognathus vituli
Haematopinus eurysternus
Damalinia bovis
Solenopotes capillatus
Horn Flies
Haematobia irritans

Persistent Activity
IVOMEC Pour-On has been proved to effectively control infections and protects cattle against reinfection with: *Dictyocaulus viviparus* and *Oesophagostomum radiatum* for 28 days after treatment; *Cooperia punctata* and *Trichostrongylus axei* for 21 days after treatment; *Ostertagia ostertagi, Haemonchus placei, Cooperia oncophora* and *Cooperia surnabada* for 14 days after treatment; *Damalinia bovis* for 56 days after treatment.

Treatment of Cattle for Horn Flies
IVOMEC Pour-On controls horn flies *(Haematobia irritans)* for up to 28 days after dosing.

n. Effect of Supplement: To add the new persistent activity indications for *Dictyocaulus viviparus* for 28 days after treatment, *Cooperia surnabada* for 14 days after treatment, and *Damalinia bovis* for 56 days after treatment. To extend the persistent activity periods for *Oesophagostomum radiatum* from 14 to 28 days after treatment and *Cooperia punctata* and *Trichostrongylus axei* from 14 days to 21 days after treatment. At this time, the labeling is being revised to reflect updated environmental information, to speciate *Cooperia* spp in the treatment and control section of the indications, and to add the veal calf warning statement to the residue information section.

2. EFFECTIVENESS

A. Dose Characterization

Effectiveness studies were presented in the original NADA 140-841 FOI Summary dated December 7, 1990, establishing the recommended effective dose of IVOMEC Pour-On for the treatment and control of internal and external parasites.

B. Substantial Evidence for Persistent Effectiveness Against Endoparasites

Five pivotal studies were conducted in the United States to evaluate the persistent activity of IVOMEC Pour-On in preventing infection of treated cattle with third stage larvae of several species of endoparasites. The studies had similar designs with separate groups of cattle receiving a daily challenge of third-stage nematode larvae 15, 21, or 28 days following treatment with ivermectin administered in its final formulation at a dose level of 0.5 mg/kg body weight. The efficacy was determined by comparing the geometric mean worm counts of the treated groups with those of an untreated control group for each parasite species present in at least six adequately infected control animals. P-values were computed for each parasite species using contrasts in a one-way analysis of variance or unequal-variance t-tests on log-transformed counts. The period of persistent activity was defined as the time during which the efficacy against a genus species was ≥ 90%.

For an indication to be granted, a minimum of two studies showing 90% efficacy was required for each genus species of parasite and at each persistent effect period. The new indication of persistent effect against *Dictyocaulus viviparus* for 28 days after treatment is supported by Trial ASR 15090 and Trial ASR 15095. The new indication for persistent effect against *Cooperia surnabada* for 14 days after treatment is supported by Trial ASR 14553 and Trial ASR 15110. The extension of the persistent effect period for *Oesophagostomum radiatum* from 14 days to 28 days is supported by Trial ASR 15110 and Trial ASR 15111. The extension of the persistent effect period for *Cooperia punctata* from 14 days to 21 days is supported by Trial ASR 15110 and Trial ASR 15111. The extension of the persistent effect period for *Trichostrongylus axei* from 14 days to 21 days is supported by Trial ASR 15110 and Trial ASR 15111. The five trials are individually summarized below.

B.1 Trial ASR 14553

1) Type of Study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

2) Investigator: Bruce N. Kunkle, D.V.M., M.S., Ph.D.
Merial Limited
Fulton, Missouri

3) General Design:

a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

b. Animals: Twenty-eight (28) crossbred female and castrated male calves (7 per group), approximately 6 months old and weighing 152 to 221 kg at the start of the study were used. All animals were treated with another anthelmintic during the acclimation period to eliminate existing infections.

c. Treatment Groups: There were 4 treatment groups. One group received IVOMEC Pour-On. The negative controls received no treatment. Two groups received medications which were not pertinent to this approval and are not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Cooperia* spp. (1000 per day for 15 days). There were larvae of other genus species given for various lengths of time that are not pertinent to this approval and are not reported. This study provided support for the 14-day persistent effect period, even though the larvae were administered for 15 days.

e. Dosage Form: The dosage form was IVOMEC Pour-On topical solution, 5 mg ivermectin/mL.

f. Route of Administration: Topical.

g. Dose: 1 mL/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test Duration: 49 to 51 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 to 51 days after treatment, 35 to 37 days after the last *Cooperia* spp. larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for 3 species of *Cooperia.* Efficacy is summarized in Table 2.1:

Table 2.1 Trial ASR 14553 - Percent Efficacy IVOMEC Pour-On 15-day Persistent Effect Period

Nematode Species	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Pour-On
Cooperia oncophora	223.3	0.5	99.8
Cooperia punctata	2949.8	0.5	99.9
Cooperia surnabada	154.2	0.5	99.6

5) Adverse Reactions: Some animals had loose stools during the trial and one animal vomited. These problems were not believed to be related to the experimental treatments.

B.2 Trial ASR 15090

1) Type of Study: Dose confirmation study in cattle with induced infections of lungworms.

2) Investigator: Edward G. Johnson, D.V.M.
Johnson Research
Parma, Idaho

3) General Design:
   a. Purpose: To determine the period after treatment during which infections of lungworms are controlled.

   b. Animals: Forty (40) Holstein intact male calves (10 per group), no more than 8 months old and weighing 183 to 278 kg at the start of the study were used. Animals were free of patent infections at the time of treatment.

   c. Treatment Groups: There were 4 treatment groups. Two groups received IVOMEC Pour-On. Two groups were negative controls that received the vehicle for IVOMEC Pour-On topically at 1 mL/10 kg body weight.

   d. Infection: Infective larvae were given to each animal daily, starting on the day after treatment, according to the following schedule: *Dictyocaulus viviparus* (50 per day for 21 or 28 days). There was a separate control and treated group for each time period.

   e. Dosage Form: The dosage form was IVOMEC Pour-On topical solution, 5 mg ivermectin/mL.

   f. Route of Administration: Topical.

   g. Dose: 1 mL/10 kg body weight (500 mcg ivermectin/kg body weight) once.

   h. Test Duration: 42 or 49 days after treatment.

   i. Pertinent Variables Measured: Worm counts were determined at necropsy, 42 days after treatment for the 21 day period or 49 days after treatment for the 28 day period, 21 days after the last *Dictyocaulus viviparus* larvae were administered for each group.

4) Results: There was an adequate level of infection in at least 6 control animals for both time periods. Efficacy is summarized in Table 2.2:

Table 2.2 Trial ASR 15090 - Percent Efficacy IVOMEC Pour-On Against *Dictyocaulus viviparus*

Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Pour-On
21 days	34.5	0	100
28 days	23.3	0.1	99.4

5) Adverse Reactions: An injured left hind leg, pinkeye, elevated temperature, dyspnea, and bloat were observed in some animals during the trial. These health problems were not believed to be related to the experimental treatments.

B.3 Trial ASR 15095

1) Type of Study: Dose confirmation study in cattle with induced infections of lungworms.

2) Investigator: Bruce N. Kunkle, D.V.M., M.S., Ph.D.
Merial Limited
Fulton, Missouri

3) General Design:

a. Purpose: To determine the period after treatment during which infections of lungworms are controlled.

b. Animals: Twenty (20) Holstein castrated male calves (10 per group), approximately 5 to 10 months old and weighing 195 to 304 kg at the start of the study were used. Animals were free of patent infections at the time of treatment.

c. Treatment Groups: There were 2 treatment groups. One group received IVOMEC Pour-On and the other group was a negative control that received the vehicle for IVOMEC Pour-On topically at 1 mL/10 kg body weight.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Dictyocaulus viviparus* (100 per day for 28 days).

e. Dosage Form: The dosage form was IVOMEC Pour-On topical solution, 5 mg ivermectin/mL.

f. Route of Administration: Topical.

g. Dose: 1 mL/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test Duration: 9 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 days after treatment, 21 days after the last *Dictyocaulus viviparus* larvae were administered.

4) Results: There was an adequate level of infection in 9 of the control animals. Efficacy is summarized in Table 2.3:

Table 2.3 Trial ASR 15095 - Percent Efficacy IVOMEC Pour-On Against *Dictyocaulus viviparus*

Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Pour-On
28 days	15.7	0	100

5) Adverse Reactions: Inappetence, loose stool, depression, and a watering right eye were observed in some animals during the trial. These health problems were bit believed to be related to the experimental treatments.

B.4 Trial ASR 15110

1) Type of Study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

2) Investigator: Edward G. Johnson, D.V.M.
Johnson Research
Parma, Idaho

3) General Design:

a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

b. Animals: Thirty (30) Holstein male calves (10 per group), approximately 4 to12 months old and weighing 130 to 186 kg at the start of the study were used. Animals were clear of patent infections at the time of treatment.

c. Treatment Groups: There were 3 treatment groups. One group received IVOMEC Pour-On. The negative controls received no treatment. One group received a medication which is not pertinent to this approval and is not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Cooperia oncophora & punctata* (1000 per day for 21 days), *Trichostrongylus axei* (500 per day for 21 days), and *Oesophagostomum radiatum* (100 per day for 28 days). There were larvae of

other genus species given for various lengths of time that are not pertinent to this approval and are not reported.

e. Dosage Form: The dosage form was IVOMEC Pour-On topical solution, 5 mg ivermectin/mL.

g. Route of Administration: Topical.

g. Dose: 1 mL/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test Duration: 49 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 days after treatment, 28 days after the last *Cooperia* spp. and *T. axei* larvae and 21 days after the last *O. radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for *C. punctata, C. surnabada, T. axei,* and *O. radiatum.* Efficacy is summarized in Table 2.4:

Table 2.4 Trial ASR 15110 - Percent Efficacy IVOMEC Pour-On 21-day or 28-day persistent effect periods

Nematode Species	Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Pour-On
C. punctata	21	1470.7	27.0	98.2
C. surnabada	21	258.7	15.0	94.2
T. axei	21	588.7	29.1	95.1
O. radiatum	28	278.8	18.0	93.4

5) Adverse Reactions: One animal was found to have subacute pneumonia at necropsy. This health problem was not believed to be related to the experimental treatments.

B.5 Trial ASR 15111

1) Type of Study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

2) Investigator: Bruce N. Kunkle, D.V.M., M.S., Ph.D.
Merial Limited
Fulton, Missouri

3) General Design:

a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

b. Animals: Thirty (30) Holstein heifer calves (10 per group), approximately 5 to 6 months old and weighing 165 to 268 kg at the start of the study were used. Animals were free of patent infections at the time of infection.

c. Treatment Groups: There were 3 treatment groups. One group received IVOMEC Pour-On. The negative controls received no treatment. One group received a medication which was not pertinent to this approval and is not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Cooperia punctata* (1000 per day for 21 days), *Trichostrongylus axei* (500 per day for 21 days), and *Oesophagostomum radiatum* (100 per day for 28 days). There were larvae of other genus species given for various lengths of time that were not pertinent to this approval and are not reported.

e. Dosage Form: The dosage form was IVOMEC Pour-On topical solution, 5 mg ivermectin/mL.

h. Route of Administration: Topical.

g. Dose: 1 mL/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test Duration: 49 or 50 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 or 50 days after treatment, 28 or 29 days after the last *Cooperia* spp. and *T. axei* larvae and 21 days after the last *O. radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for *C. punctata, T. axei,* and *O. radiatum*. Efficacy is summarized in Table 2.5:

Table 2.5 Trial ASR 15111 - Percent Efficacy IVOMEC Pour-On 21-day or 28-day persistent effect periods

Nematode Species	Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Pour-On
C. punctata	21	2917.8	1.8	99.9
T. axei	21	2122.8	1.5	99.9
O. radiatum	28	174.2	1.7	99.0

5) Adverse Reactions: Soft stool, bloody stool, abdominal swelling, nasal discharge, depressed appetite, and elevated temperature were observed in three nonmedicated control animals during the trial. These health problems were not believed to be related to the experimental treatments.

C. Substantial Evidence for Persistent Effectiveness Against *Damalinia bovis*

Two pivotal studies were conducted in the United States to evaluate the persistent activity of IVOMEC Pour-On in preventing infestation of treated cattle with *Damalinia bovis*. The studies had similar designs with separate groups of lice-free cattle being exposed to infested cattle for either 42 to 49 days after treatment or 49 to 56 days after treatment with ivermectin administered in its final formulation at a dose level of 0.5 mg/kg body weight. The efficacy was determined by comparing the geometric mean lice counts of the treated groups with those of an untreated control group on two separate count days post introduction of infested cattle. An adequate level of infestation had to be present in at least six infested control animals in order for the study to be acceptable. Lice counts were transformed to the natural logarithm (count + 1) for calculation of the geometric means. Treated and control groups were compared at each post-treatment time point using Wilcoxon's rank sum test. The period of persistent activity was defined as the time during which the efficacy against lice was demonstrated to be ≥ 90%.

For an indication to be granted, a minimum of two studies showing 90% efficacy was required at each persistent effect period. The new indication of persistent effect against *Damalinia bovis* for 56 days after treatment is supported by Trial Number PR&D 0045401 and Trial Number PR&D 0045402. The two trials are individually summarized below.

C.1 Trial Number PR&D 0045401

1) Type of Study: Dose confirmation study in cattle with natural infestations of lice.

2) Investigator: K.E. Sterner, B.S., D.V.M.
Sterner Veterinary Clinic
Ionia, Missouri

3) General Design:

   a. Purpose: To evaluate the persistence of effect of topically administered ivermectin at 500 mcg/kg body weight to prevent the establishment of lice (*Damalinia bovis*) by natural transfer.

   b. Animals: Thirty (30) louse-free female Holstein calves, approximately 6 months old and weighing 119 to 244 kg on Day -1 were used as principle animals. Thirty (30) female and male castrate Holstein or Holstein crossbred calves, weighing 124 to 243 kg on Day 48 were used as donor animals. To ensure the principle animals were free of lice, they were treated topically with Vapona spray on Days -19 and -5 according to the manufacturer's recommendations and were free of lice as confirmed by a pretreatment examination on Day 0.

c. Treatment Groups: There were 3 treatment groups. Two groups received IVOMEC Pour-On, one on Day 0 and the other on Day 7. The negative control group received a placebo vehicle that resembled the appearance of the test drug.

d. Infestation: Each principal animal was naturally infested by exposure to donor cattle shown to have infestations of *Damalinia bovis*. Beginning on Day 49, each principal animal was exposed to one donor animal for 7 days. Following exposure, donor animals were removed on Day 56.

e. Dosage Form: The dosage form was IVOMEC Pour-On topical solution, 5 mg ivermectin/mL.

i. Route of Administration: Topical.

g. Dose: 1 mL/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test Duration: 84 days after treatment.

i. Pertinent Variables Measured: Lice counts were conducted on principal animals on Days 70 and 84 to ensure sufficient time for any lice successfully transferred to become established. These counts at each time point were calculated for each animal by summing the counts from 12 predilection sites.

4) Results: There was an adequate level of infestation in at least 6 control animals for *Damalinia bovis.* Efficacy is summarized in Table 2.6:

Table 2.6 Trial Number PR&D 0045401 - Percent Efficacy IVOMEC Pour-On Against *Damalinia bovis*

Challenge Period[1]	Count Day	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Pour-On	P-value[2]
42 to 49 days	70	23.0	0.0	100	<0.0001
42 to 49 days	84	44.4	0.0	100	<0.0001
49 to 56 days	70	23.0	0.0	100	<0.0001
49 to 56 days	84	44.4	0.0	100	<0.0001

[1]Days after treatment that principal animals were exposed to donor animals. Cattle treated on Day 0 were challenged 49 to 56 days after treatment and cattle treated on Day 7 were challenged on 42 to 49 days after treatment.
[2]The p-value represents the exact probability of a statistical difference between the treatment group and the control group using the Wilcoxin rank sum test in SAS.

5) Adverse Reactions: No treatment related health problems were observed.

C.2 Trial Number PR&D 0045402

1) Type of Study: Dose confirmation study in cattle with natural infestations of lice.

2) Investigator: J.E. Holste, D.V.M.
Merial Limited
Fulton, Missouri

3) General Design:

a. Purpose: To evaluate the persistence of effect of topically administered ivermectin at 500 mcg/kg body weight to prevent the establishment of lice (*Damalinia bovis*) by natural transfer.

b. Animals: Thirty (30) louse-free female Holstein calves, approximately 6 months old and weighing 173 to 224 kg on Day -1 were used as principle animals. Thirty (30) female and male intact and castrate Holstein or Holstein crossbred calves, weighing 91 to 257 kg on Day 48 were used as donor animals. To ensure the principal animals were free of lice, they were treated topically with Vapona spray on Days -19 and -5 according to the manufacturer's recommendations and were free of lice as confirmed by a pretreatment examination on Day 0.

c. Treatment Groups: There were 3 treatment groups. Two groups received IVOMEC Pour-On, one on Day 0 and the other on Day 7. The negative control group received a placebo vehicle that resembled the appearance of the test drug on Day 7.

d. Infestation: Each principal animal was naturally infested by exposure to donor cattle shown to have infestations of *Damalinia bovis*. Beginning on Day 49, each principal animal was exposed to one donor animal for 7 days. Following exposure, donor animals were removed on Day 56. Counts were conducted on principal animals on Days 70 and 84 to ensure sufficient time for any lice successfully transferred to become established.

e. Dosage Form: The dosage form was IVOMEC Pour-On topical solution, 5 mg ivermectin/mL.

j. Route of Administration: Topical.

g. Dose: 1 mL/10 kg body weight (500 mcg ivermectin/kg body weight) once.

h. Test Duration: 84 days after treatment.

i. Pertinent Variables Measured: Lice counts conducted on principal animals on Days 70 and 84 were calculated for each animal by summing the counts from 12 predilection sites.

4) Results: There was an adequate level of infestation of *Damalinia bovis* in at least 6 control animals on both count days. Efficacy is summarized in Table 2.7:

Table 2.7 Trial Number PR&D 0045402 - Percent Efficacy IVOMEC Pour-On Against *Damalinia bovis*

Challenge Period[1]	Count Day	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Pour-On	P-value[2]
42 to 49 days	70	133.7	0.0	100	<0.0001
42 to 49 days	84	139.1	0.0	100	<0.0001
49 to 56 days	70	133.7	0.0	100	<0.0001
49 to 56 days	84	139.1	0.0	100	<0.0001

[1]Days after treatment that principal animals were exposed to donor animals. Cattle treated on Day 0 were challenged 49 to 56 days after treatment and cattle treated on Day 7 were challenged on 42 to 49 days after treatment.
[2]The p-value represents the exact probability of a statistical difference between the treatment group and the control group using the Wilcoxin rank sum test in SAS.

5) Adverse Reactions: No treatment related health problems were observed.

3. TARGET ANIMAL SAFETY

No further target animal safety data were required from the original approval as discussed in the parent NADA 140-841 FOI Summary dated December 4, 1990.

4. HUMAN SAFETY

No further human food safety data were required from the original approval as discussed in the parent NADA 140-841 FOI summary dated December 4, 1990 and in the supplement to NADA 128-409 FOI summary (IVOMEC Injection for Cattle) dated September 12, 1994. There is a 48-day withdrawal period for slaughter, a withdrawal period for milk has not been established, and a withdrawal period has not been established for pre-ruminating calves.

5. AGENCY CONCLUSIONS

The data submitted in support of this supplemental 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 (ivermectin) Pour-On for Cattle when administered once at 500 mcg/kg body weight is safe and effective for the addition of the following new persistent effect indications: *Dictyocaulus viviparus* for 28 days, *Cooperia surnabada* for 14 days, and *Damalinia bovis* for 56 days. Also, the persistent effect periods are extended for the following: *Oesophagostomum radiatum* from 14 to 28 days and *Cooperia punctata* and *Trichostrongylus axei* from 14 days to 21 days.

The following has been added to the residue information section of the labeling, "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal."

The Agency has concluded that this product retain over-the-counter marketing status because adequate directions for use have been written for the layperson and the conditions of use prescribed on the label are likely to be followed in practice.

In accordance with 21 CFR 514.106(b)(2)(v), this is a Category II change which did not require a reevaluation of the safety or effectiveness data in the parent application.

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the new persistent effect indications and the extension of 3 already approved persistent effect indications listed above.

No patent information was submitted with this application.

6. ATTACHMENTS

Facsimile Labeling is attached as indicated below:

A. 250 mL – Leaflet front (Page 1 and 2), label front, carton

B. 1 L – Leaflet, front and base, carton

C. 2.5 and 5 L – Label front and back, carton

D. 20 L – label front and back, outsert front and back (page 1 and 2)

E. Package insert for all container sizes