Date of Approval: July 1, 2019

CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-639

Monovet® 90

monensin Type A medicated article

Type A medicated article to be used in the manufacture of Type B and Type C medicated feeds

Cattle and Goats

Cattle fed in confinement for slaughter: for improved feed efficiency; for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*. Dairy cows: for increased milk production efficiency (production of marketable solids-corrected milk per unit of feed intake). Growing cattle on pasture or in dry lot (stocker and feeder and dairy and beef replacement heifers): for increased rate of weight gain; for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*. Mature reproducing beef cows: for improved feed efficiency when receiving supplemental feed; for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*. Calves (excluding veal calves): for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*. Goats: for the prevention of coccidiosis caused by *Eimeria crandallis*, *Eimeria christenseni*, and *Eimeria ninakohlyakimovae* in goats maintained in confinement.

Sponsored by:

Huvepharma EOOD

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I. GENERAL INFORMATION

A. File Number

ANADA 200-639

B. Sponsor

Huvepharma EOOD
5th Floor, 3A Nikolay Haytov Str.
1113 Sofia, Bulgaria

Drug Labeler Code: 016592

US Agent Name and Address:
Kelly Beers, Ph.D.
Huvepharma, Inc.
525 West Park Drive
Peachtree City, GA 30269

C. Proprietary Name

Monovet® 90

D. Drug Product Established Name

monensin Type A medicated article

E. Pharmacological Category

Ionophore, anticoccidial

F. Dosage Form

Type A medicated article to be used in the manufacture of Type B and Type C medicated feeds.

G. Amount of Active Ingredient

90.7 g/lb (200 g/kg)

H. How Supplied

25 kg (55.12 lb) bags

I. Dispensing Status

OTC

J. Dosage Regimen

1. **Cattle fed in confinement for slaughter:**

    a. **For improved feed efficiency:** Feed complete feed (5 to 40 g/ton) continuously to growing finishing beef cattle to provide not less than 50 nor more than 480 mg monensin per head per day.

b. **For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*:** Feed continuously (10 to 40 g/ton) to provide 0.14 to 0.42 mg per pound of body weight per day, depending upon severity of challenge, up to a maximum of 480 mg of monensin per head per day.

2. **Dairy Cows:**

   a. **For increased milk production efficiency (production of marketable solids-corrected milk per unit of feed intake):**

      i. Total Mixed Rations ("complete feed"): Feed continuously to dry and lactating dairy cows a total mixed ration ("complete feed") containing 11 to 22 g/ton monensin on a 100% dry matter basis.
      ii. Component Feeding Systems (including top dress): Feed continuously to dry and lactating dairy cows a Type C Medicated Feed containing 11 to 400 g/ton monensin. The Type C Medicated Feed must be fed in a minimum of 1 pound of feed per cow per day to provide 185 to 660 mg/head/day monensin to lactating cows or 115 to 410 mg/head/day monensin to dry cows.

3. **Growing cattle on pasture or in dry lot (stocker and feeder and dairy and beef replacement heifers):**

   a. **For increased rate of weight gain:** Feed at the rate of not less than 50 nor more than 200 mg per head per day in not less than one pound of Type C Medicated Feed; or after the 5th day, feed at the rate of 400 mg per head per day every other day in not less than 2 pounds of Type C Medicated Feed. The monensin concentration in the Type C Medicated Feed must be between 15 and 400 grams per ton. During the first 5 days, cattle should receive no more than 100 mg per day contained in not less than 1 pound of feed. Do not self feed.

   b. **For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*:** Feed at a rate to provide 0.14 to 0.42 mg per pound body weight per day, depending upon severity of challenge, up to a maximum of 200 mg per head per day. The monensin concentration in Type C Medicated Feed must be between 15 and 400 grams per ton. During the first 5 days, cattle should receive no more than 100 mg per day contained in not less than 1 pound of feed.

   c. **Free-Choice (Self-Fed) Medicated Feeds:** All Free-choice medicated feeds must provide not less than 50 nor more than 200 mg monensin per head per day.

4. **Mature Reproducing Beef Cows (on pasture or in dry lot):**

   a. **For improved feed efficiency when receiving supplemental feed:** Feed continuously at a rate of 50 to 200 mg per head per day. Blend into a minimum of 1 pound of Type C Medicated Feed and either hand feed or mix into the total ration. Feed (other than the Type C Medicated Feed containing Monovet® 90) can be restricted to 95% (of normal requirements) when 50 mg of monensin activity is fed, and to 90% at

200 mg. Cows on pasture or in dry lot must receive a minimum of 1 pound of Type C Medicated Feed per head per day. Additionally, a minimum of 16 pounds (air-dry basis) of roughage such as silage, haylage, ammoniated straw, hay or equivalent feedstuffs should be fed in order to meet NRC recommendations for mature reproducing beef cows to gain 0.25 to 0.75 pounds per head per day. Standing, dried winter range forage may not be of adequate quality to result in improved efficiency when supplemented with Monovet® 90. During the first 5 days, pastured cattle should receive no more than 100 mg per day contained in not less than 1 pound of feed. Do not self feed.

b. **For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*:** Feed at a rate of 0.14 to 0.42 mg per pound of body weight per day, depending upon severity of challenge, up to a maximum of 200 mg per head per day. During the first 5 days, pastured cattle should receive no more than 100 mg per day contained in not less than 1 pound of feed.

5. **Goats:**

a. **For prevention of coccidiosis caused by *Eimeria crandallis*, *Eimeria christenseni*, and *Eimeria ninakohlyakimovae*:** Feed complete feed (20 g/ton) continuously to goats as the sole ration. Feed only to goats maintained in confinement.

6. **Calves (excluding veal calves):**

a. **For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*:** Feed at a rate of 0.14 to 1.00 mg per pound of body weight per day, depending upon severity of challenge, up to a maximum of 200 mg of monensin per head per day. The monensin concentration in Type C Medicated Feed must be between 10 and 200 g/ton.

K. Route of Administration

Oral

L. Species/Class

Cattle fed in confinement for slaughter, dairy cows, growing cattle on pasture or in dry lot (stocker and feeder and dairy and beef replacement heifers), mature reproducing beef cows, calves (excluding veal calves), and goats

M. Indications

Cattle fed in confinement for slaughter:

1. For improved feed efficiency.
2. For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*.

Dairy Cows:

1. For increased milk production efficiency (production of marketable solids-corrected milk per unit of feed intake).

Growing cattle on pasture or in dry lot (stocker and feeder and dairy and beef replacement heifers):

1. For increased rate of weight gain.
2. For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*.

Mature Reproducing Beef Cows:

1. For improved feed efficiency when receiving supplemental feed.
2. For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*.

Goats:

1. For the prevention of coccidiosis caused by *Eimeria crandallis*, *Eimeria christenseni*, and *Eimeria ninakohlyakimovae* in goats maintained in confinement.

Calves (excluding veal calves):

1. For the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*.

N. Reference Listed New Animal Drug

Rumensin™ 90; monensin Type A medicated article; NADA 095-735; Elanco US Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug. The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is demonstrated through a clinical end-point study in a food producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

Monovet® 90 was determined to be bioequivalent to the RLNAD (Rumensin™ 90) using an approach that included a comparison of product similarity and *in vivo* and *in vitro* studies. The comparison of product similarity included an assessment of the qualitative (Q1), quantitative (Q2) and physicochemical (Q3) attributes of Monovet® 90 to show that the generic product is compositionally and structurally equivalent to the RLNAD. An *in vivo* clinical end-point bioequivalence study in cattle for the indication of feed efficiency demonstrated a bioequivalent clinical effect of Monovet® 90 to the RLNAD. The RLNAD is locally acting within the gastrointestinal tract for all approved indications, thus dissolution is considered the critical attribute which impacts the availability of monensin at the site of action. Based on this knowledge of the activity of monensin combined with data demonstrating that Monovet® 90's formulation was Q1, Q2, and Q3 equivalent to the RLNAD and that it had an equivalent clinical effect within the gastrointestinal tract, bioequivalence for the additional approved indications was sufficiently demonstrated through *in vitro*

comparative dissolution across a range of conditions consistent with those encountered in the target species gastrointestinal tract.

A. Evaluation of Product Similarity (Q1, Q2 and Q3 Sameness):

To support sameness of Monovet® 90 Type A medicated article to the RLNAD, data were provided to confirm that the test and RLNAD formulations contain the same active ingredient in the same amount, that no inactive ingredients significantly affect the bioavailability of the active ingredient, and that the test product is manufactured in a manner that results in comparable physicochemical properties to the RLNAD. The following attributes were confirmed:

1. Monovet® 90 contains the same active ingredient in the same concentration and dosage form as the RLNAD and contains no inactive ingredients that may significantly affect the bioavailability of the active pharmaceutical ingredient. Monovet® 90 is considered qualitatively (Q1) and quantitatively (Q2) equivalent to the RLNAD.

2. Monovet® 90 and the RLNAD were determined to be physiochemically (Q3) equivalent based on acceptable comparative characterization of three batches of Monovet® 90 and five batches of the RLNAD. The physiochemical tests chosen for these comparisons were those that are most likely to affect the quality and performance of the Type A medicated article. The characterization of Monovet® 90 and the RLNAD included the following comparisons of the critical control attributes:

    a. Compendial testing as indicated in the United States Pharmacopeia (USP):

        i. Identification to demonstrate that the correct active pharmaceutical ingredient (API) is present in both products.

        ii. Assay (quantity of monensin A, monensin B, and monensin C/D)[1] to demonstrate that the API is present at the labeled potency and that the various components of monensin A, B, and C/D meet the requirements indicated in the USP monograph for monensin Type A medicated articles.

        iii. Loss on drying to demonstrate that moisture levels in each product is less than the USP limit.

    b. Impurities were assessed in extracts of the Monovet® 90 and Rumensin™ 90 drug products and the monensin API for Monovet® 90. Impurities levels in Monovet® 90 were assessed to ensure that no impurities were introduced at levels that would impose a safety concern when compared to the RLNAD.

    c. Particle size distribution over a 100 – 800 µm range. This attribute ensures even distribution of the Type A medicated article in the finished feed. In addition, the particle size distributions must be comparable for

[1] Monensin consists of a mixture of components as described in the USP monograph for monensin Type A medicated articles. Monensin A and monensin B are considered to be the predominant components with a minor component comprised of monensin C/D.

the test article to have an equivalent rate and extent of dissolution of the API from the matrix of the Type A medicated article.

Based on the comparisons discussed above, we determined that Monovet® 90 is qualitatively (Q1), quantitatively (Q2), and physiochemically (Q3) equivalent to the RLNAD.

B. Clinical End-point Bioequivalence Study:

To support bioequivalence when a Type A medicated article contains an active pharmaceutical ingredient (API) whose effect site is locally acting within the gastrointestinal tract, a clinical end-point study is necessary. This is because a blood-level pharmacokinetic study is not possible for a locally acting, poorly soluble API which does not undergo systemic absorption. A clinical end-point study should be conducted for each species for which the RLNAD is approved with the exception of minor species[2]. Further, the purpose of a clinical end-point bioequivalence study is not to repeat an effectiveness study intended to determine the dose-effect relationship of a drug, but rather, the purpose is to detect any formulation difference between the generic product and the reference listed new animal drug (RLNAD) with respect to bioavailability of the API. Because an evaluation of Q1, Q2, and Q3 attributes, as well as a comparative dissolution study, demonstrated formulation sameness between the RLNAD and the proposed generic product, a single *in vivo* study for one approved indication for the RLNAD was sufficient to support a conclusion of bioequivalence. For this approval, a clinical end-point study was conducted to demonstrate equivalence between the generic and RLNAD products for feed efficiency in crossbred beef steers.

1. Study Title: A Clinical End-point (Feed Efficiency) Bioequivalence Study of Type A Medicated Articles in Type C Medicated Feeds in Cattle Fed in Confinement for Slaughter.

2. Study Number: H1701BB

3. Study Standard: Good Laboratory Practices (GLP)

4. Study Objective: To assess the bioequivalence between the generic monensin Type A medicated article versus the RLNAD in cattle fed in confinement for slaughter.

5. Study Design: This was a single-site, masked, placebo-controlled, randomized, nonclinical laboratory study performed in 598 crossbred beef steers. The study involved three treatment groups fed Type C medicated feed throughout the treatment phase (days 0-112) of the study. The treatment groups consisted of a negative control article (placebo), a positive control article (the RLNAD) fed at 30 g/ton, and a test article (Monovet® 90) fed at 30 g/ton. Each treatment group was housed in 20 pens containing 10 animals each with the exception of 2 pens that contained 9 animals each. Animals were weighed prior to day -26,

[2] In alignment with the November 2006 Guidance for Industry #35, Bioequivalence Guidance, "a bioequivalence study generally should be conducted for each species for which the pioneer product is approved on the label, with the exception of minor species [as defined in section 516.3(b) of Title 21 of the Code of Federal Regulations] on the label."

on day -1 and on day 112, prior to the day's feeding. There were 2 animals from the negative control article group that died of bloat after day zero and were also weighed. Animals were fed *ad libitum* once daily the appropriate feed for their assigned group. Feed-to-gain ratio (feed efficiency) on a 90% dry matter basis was the primary clinical end-point for the determination of bioequivalence.

Table II.1. A summary of treatment groups for study number H1701BB

Total # of Animals	# of Pens	Animals per Pen	Type of feed	Duration
200	20	10	Type C feed containing negative control article (placebo)	112 days
198	20	9 or 10*	Type C medicated feed containing positive control article (RLNAD)	
200	20	10	Type C medicated feed containing test article (generic)	

*Two animals, each from a different pen, were excluded on day zero and were not replaced due to unavailability of suitable replacement animals.

6. Study Location: A commercial feedlot in Idaho.

7. Study Duration: 112 days on treatment; 113 days in pen.

8. Study Animals: Crossbred beef steers, 8 -12 months of age (estimate) were used in this study. The average weight of the study animals on day 112 was within the typical market weight range for feedlot cattle. Animals appearing to be of high continental or *Bos indicus* influence were excluded from the study. The animals were housed in a commercial feedlot.

9. Test Article: Monovet® 90 (monensin Type A medicated article)

10. Reference Article: Rumensin™ 90 (monensin Type A medicated article)

11. Study Dates: July 31, 2017 – May 18, 2018

    a. Animal selection: July 31, 2017

    b. Cohort 1: August 30, 2017 (beginning of treatment period) - December 20, 2017 (end of treatment period)

    c. Cohort 2: August 31, 2017 (beginning of treatment period) – December 21, 2017 (end of treatment period)

12. Measurements:

    a. Body weight gain

    b. Average daily weight gain

    c. Average daily feed consumption

13. Animal Health Observations: Abnormal health observations were minimal for each treatment group and were considered commonplace in the feedlot industry.

14. Statistical Analysis: The primary outcome for analysis was the feed-to-gain ratio (feed efficiency) on a 90% dry matter basis. An analysis of variance (ANOVA) using the PROC MIXED procedure in SAS was conducted. The model included treatment as a fixed effect and initial pen weight as a covariate. Blocks were included as a random effect. The least square means (LSMEANS) statement with the DIFF option was used to provide pairwise comparisons among the treatment means.

    To demonstrate adequate sensitivity, the comparisons of each medicated feed treatment to the negative control article must be statistically significant (α=0.05, 2-sided) and show numerical superiority to negative control. The bioequivalence of Monovet® 90 and the RLNAD was evaluated using a 90% confidence interval constructed about the ratio of the mean for Monovet® 90 divided by the mean for the RLNAD. The 90% confidence interval about the ratio of means was constructed using the method of Fieller's Theorem. Bioequivalence was based on whether the limits of the 90% confidence interval about the ratio were contained within [0.80, 1.25].

15. Results: Both the groups fed Monovet® 90 and the RLNAD had significantly different and higher feed efficiency than the negative control article ($p<0.05$).

    Table II.2. Summary of the bioequivalence evaluation for feed efficiency (feed to gain ratio)

Treatment group	Least Square Means	Standard Error of the Mean
Un-medicated feed[1]	9.3496	0.09078
RLNAD	8.4824*	0.09112
Test Article	8.4005*	0.09058

[1]Negative control (placebo)
*Significantly different ($p<0.05$) in comparison to the negative article

    The ratio of the means of Monovet® 90 to the RLNAD was 0.99 and the 90% confidence interval was [0.97, 1.02] which was contained within [0.80, 1.25].

16. Conclusions: The data from study H1701BB indicate that the API in Monovet® 90 is available at the same rate and extent at its site of action in cattle (the rumen) as that of the RLNAD. The ratio of the means of Monovet® 90 to the

RLNAD was 0.99 and the 90% confidence interval was [0.97, 1.02]. This was contained within confidence interval acceptance criteria for bioequivalence of [0.80, 1.25]. The bioequivalence for the claim of feed efficiency between Monovet® 90 and the RLNAD was established.

C. Comparative *In Vitro* Dissolution Study:

An *in vitro* dissolution study was performed to demonstrate the comparability of *in vitro* release profiles in terms of their respective rates and extent of API release using 5 lots of the RLNAD and 3 lots of Monovet® 90 across a range of *in vitro* conditions consistent with those encountered in the target species gastrointestinal tract.

1. *In vitro* Dissolution Study:

   a. Study Title: Comparative dissolution of Monovet® 90 and Rumensin™ Type A medicated articles

   b. Study Standard: Good Laboratory Practices (GLP)

   c. Study Objective: To demonstrate the sameness of the rate and extent of API release of Huvepharma's Monovet® 90 (monensin Type A medicated article) and Elanco's Rumensin™ 90 (monensin Type A medicated article), using comparative *in vitro* dissolution.

   d. Test Article: Three (3) lots of Monovet® 90 (monensin Type A medicated article).

   e. Reference Article: Five (5) lots of Rumensin™ 90 (monensin Type A medicated article).

   f. Dissolution Parameters: *In vitro* dissolution testing was conducted using USP Type II apparatus (paddle).

Table II.3. General parameters for the dissolution vessels

Parameter	Description
Volume	900 mL ± 1.0%
Mass of TAMA*	45.0 ± 0.1 mg
Concentration	10 mg monensin/L as biopotency based on label claim
Temperature	38 °C ± 0.5 °C,
pH	Within ± 0.1 of the intended pH
Sample Points (minutes)	30, 60, 90, 120, 240, 360, 480 and 600
Paddle Speed	75 or 50 rpm as specified for condition

*Type A medicated article.

The test article concentration was set to satisfy sink condition requirements. Sampling points and test duration were established so that at least one lot of the RLNAD product from at least one test condition achieved >85% dissolution.

Dissolution Conditions: Three test conditions utilized in the study were, respectively TC-1, TC-2 and TC-3, which represented a combination of USP

Buffers with Tween 80, of pH 4.6 and 7.5 with paddle speeds of 75 and 50 rpms.

g. Experimental Conditions: The following conditions were applicable to the conduct of the pivotal comparative dissolution study:

   i. The analytical method for the analysis of monensin components was determined to be adequately validated.

   ii. One of the test conditions achieved ≥ 85% dissolution and was considered to be the pivotal dissolution condition.

   iii. The pivotal dissolution condition was determined to be discriminative.

   iv. The rate of release of monensin A was determined to be correlated to the rate of release of monensin B (f_2 ≥50). Therefore, the rate of release of monensin A was used as the pivotal measured parameter.

   v. Test conditions at pH values less than 4.6 were excluded from the study because of monensin degradation.

2. Establishing Tolerance Limits: Product comparisons were based upon the tolerance limit (TL) approach developed by Martinez and Zhao, 2018[3]. This approach integrates a statistical confidence into the determination of tolerance limits about the RLNAD product profile. The assessment was conducted in two stages:

   a. Stage 1:

      Confirmation that the average percent dissolved versus time profiles are comparable by demonstrating that the f2' metric[4] is 50 or greater across all conditions under which *in vitro* dissolution was evaluated.

   b. Stage 2:

      Determination of the TL about the reference profile: The 99% TL, estimated with 95% confidence, was calculated for the RLNAD product at each sampling time. In addition, the allowable deviations about the target value (Q) were defined as follows in terms of level - S1 and level - S2 acceptance criteria using the 99% TL with 95% confidence at each sampling time.

      Level - S1: Q ± 5% at each sampling time.

      Level - S2: Q ± 15% at each sampling time.

[3] Marilyn N Martinez and Xiongce Zhao. A Simple Approach for Comparing the *In Vitro* Dissolution Profiles of Highly Variable Drug Products: a Proposal. The AAPS Journal (2018) 20:78.

[4] The f2 metric differs from the f2' metric in that the f2 metric has variability constraints as documented in CDERs Dissolution guidance "Dissolution Testing of Immediate Release Solid Oral Dosage Forms", August 1997 which states for the use of the f2 metric "To allow the use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%." These constraints in variability do not apply to the use of the f2' metric.

To determine comparability, the individual observations for the test product were examined to ensure that the following equivalence criteria were met.

1. No more than one out of 12 test product dissolution profiles are permitted to contain percent dissolved values that fall outside the bounds defined by the reference product, Level - S1 value.

2. To be considered equivalent, none of the test product profiles are permitted to contain percent dissolved values that are outside of the bounds defined by Reference product, Level - S2 value.

c. Dissolution comparison results:

i. Stage 1 Results: In all cases the normalized data resulted in f_2' sameness criteria of ≥ 50. For the test conditions that did not attain 85% dissolution, the dissolution data (percent release of monensin) was normalized with the maximum dissolution attained assigned a value of 100% and the remaining data adjusted proportionately.

Table II.4. results of f_2' used for comparison of dissolution

Test condition	f2′
	QA
TC1	80.85
TC2	56.42
TC3	70.10

QA = monensin A

ii. Stage 2 Results: All data across the three *in vitro* methods of product assessment successfully met the criteria for profile comparability based upon the TL approach.

Evaluation of dissolution curves: The dissolution curves for both Monovet® 90 and the RLNAD were plotted graphically and evaluated for each test condition. All dissolution curves for Monovet® 90 were within the bounds established by the dissolution curves generated for the RLNAD, under identical test conditions.

Table II.5. A summation of the 99% tolerance limits (TLs) with 95% confidence level (99-95 TL) for test condition 1

Time point	RLNAD: Lower TL, Upper TL (99-95 TL)	Test Article (TA) Monovet® 90 (n=36) % Dissolution min, max	TA values contained in TL limits?
30 min	13.0, 43.8	24.8, 33.0	Yes
60 min	18.7, 60.7	36.6, 42.5	Yes
90 min	22.4, 70.0	44.4, 52.0	Yes
120 min	27.7, 78.1	50.5, 59.0	Yes
240 min	39.7, 92.9	64.9, 75.8	Yes
360 min	49.5, 99.7	72.9, 84.3	Yes
480 min	56.6, 103.8	77.5, 89.2	Yes
600 min	61.5, 107.9	81.5, 92.1	Yes

Table II.6. A summation of the 99% tolerance limits (TLs) with 95% confidence level (99-95 TL) for test condition 2

Time point	Lower TL, Upper TL (99-95 TL)	Test Article (TA) Monovet® 90 (n=36) % Dissolution min, max	TA values contained in TL limits?
30 min	7.0, 34.2	20.6, 27.2	Yes
60 min	13.7, 46.9	30.9, 39.2	Yes
90 min	18.8, 54.0	36.9, 48.6	Yes
120 min	23.1, 58.9	43.1, 53.7	Yes
240 min	34.0, 72.0	53.2, 65.7	Yes
360 min	39.4, 81.0	63.6, 75.1	Yes
480 min	45.1, 86.7	63.9, 78.3	Yes
600 min	49.1, 93.5	67.7, 81.4	Yes

Table II.7. A summation of the 99% tolerance limits (TLs) with 95% confidence level (99-95 TL) for test condition 3

Time point	Lower TL, Upper TL (99-95 TL)	Test Article (TA) Monovet® 90 (n=36) % Dissolution min, max	TA values contained in TL limits?
30 min	17.9, 36.9	20.4, 24.7	Yes
60 min	27.2, 50.4	30.7, 37.1	Yes
90 min	37.0, 55.2	38.1, 45.8	Yes
120 min	42.6, 61.2	44.0, 53.5	Yes
240 min	56.2, 76.2	59.1, 68.7	Yes
360 min	65.2, 84.0	67.5, 78.2	Yes
480 min	71.8, 89.0	73.5, 82.4	Yes
600 min	74.7, 94.7	77.2, 87.6	Yes

Dissolution profiles of 60 samples from five lots of Rumensin™ 90 were analyzed to establish the tolerance limits that sufficiently define the variability of dissolution in the approved RLNAD. The dissolution profiles of 36 samples from 3 lots of Monovet® 90 all fell within the tolerance limits established from

the RLNAD data. The *in vitro* dissolution characteristics of the generic and RLNAD products met the criteria for equivalence of formulations and were determined to be comparable with respect to their respective rates and extent of API release across a range of *in vitro* conditions.

The cumulative data supports the bioequivalence between Monovet® 90 and the RLNAD. Both formulations contain the same active ingredient in the same concentration and dosage form. Further, Monovet® 90 does not contain any additional excipients or other differences in formulation from the RLNAD that may significantly affect the bioavailability of the active ingredient, and the physicochemical properties of Monovet® 90 are comparable to the RLNAD. Both formulations release monensin at the same rate and extent across a range of *in vitro* (dissolution) conditions, and both formulations have been shown to be bioequivalent under *in vivo* (clinical end-point bioequivalence study) conditions using an approved indication for the RLNAD in cattle. The proposed product is considered bioequivalent to the RLNAD.

III. HUMAN FOOD SAFETY

The toxicological safety and the microbial food safety of the active ingredient in generic new animal drugs, such as Monovet® 90, are established during the approval of the RLNAD. Also, the codified tolerances established for the RLNAD apply to the generic new animal drug, once bioequivalence to the RLNAD is established. Therefore, for generic new animal drugs, such as Monovet® 90, Human Food Safety is assessed by a residue chemistry evaluation that establishes when residue concentrations in edible tissues and milk are less than the codified tolerance after administration of the drug (*i.e.*, safe for human consumption).

For the approval of Monovet® 90, the Agency reviewed three studies during the Human Food Safety evaluation. These studies demonstrated that monensin residues are less than the codified tolerances in edible cattle and goat tissues at 0 days after treatment with Monovet® 90 and in cow's milk at 0 days after treatment with Monovet® 90. An analytical method for monitoring residues of monensin in edible tissues and milk was developed during the approval of the RLNAD and is available.

The following are assigned to this product for cattle and goats:

A. Acceptable Daily Intake and Tolerances for Residues

The acceptable daily intake (ADI) for total residues of monensin is 12.5 micrograms *per* kilogram of body weight *per* day. The tolerances established for the RLNAD apply to the generic product. A tolerance of 0.10 parts *per* million (ppm) is established for residues of monensin (the marker residue) in cattle liver, 0.05 ppm in cattle muscle, kidney and fat, and 0.05 ppm in edible goat tissues, under 21 CFR 556.420.

B. Withdrawal Periods

The Agency evaluated three studies to assign the following withdrawal periods and milk discard times to Monovet® 90:

- Withdrawal Periods

- Cattle: 0-day withdrawal period for cattle fed Monovet® 90 according to the following conditions of use:
  - Cattle fed in confinement for slaughter: fed as a Type C medicated feed containing 5 to 40 g monensin/ton at a rate of 50 to 480 mg monensin/head/day
  - Cattle fed in confinement for slaughter: fed as a Type C medicated feed containing 10 to 40 g monensin/ton at a rate of 0.14 to 0.42 mg monensin/pound of body weight/day up to 480 mg monensin/head/day
  - Growing cattle on pasture or in dry lot: fed as a Type C medicated feed containing 15 to 40 g monensin/ton at a rate of 50 to 200 mg monensin/head/day or 400 mg monensin/head/day every other day or 0.14 to 0.42 mg monensin/pound body weight/day up to 200 mg monensin/head/day
  - Growing cattle on pasture or in dry lot: fed as a free-choice Type C medicated feed at a rate of 50 to 200 mg monensin/head/day
  - Growing cattle on pasture or in dry lot: fed as a free-choice Type C medicated feed formulated as mineral granules containing 1,620 g monensin/ton at a rate of 50 to 200 mg monensin/head/day
  - Mature reproducing beef cows: fed as Type C medicated feed containing 25 to 400 g monensin/ton at a rate of 50 to 200 mg monensin/head/day or 0.14 to 0.42 mg monensin/pound body weight/day up to 200 mg monensin/head/day
  - Calves (excluding veal calves): fed as a Type C medicated feed containing 10 to 200 g monensin/ton at a rate of 0.14 to 1.0 mg monensin/pound body weight/day up to 200 mg monensin/head/day
  - Dry and lactating dairy cows: fed as a total mixed ration Type C medicated feed containing 11 to 22 g monensin/ton
  - Dry and lactating dairy cows: fed as a component Type C medicated feed containing 11 to 400 g monensin/ton at a rate of 115 to 400 mg monensin/head/day to dry cows or 185 to 660 mg monensin/head/day to lactating dairy cows
- Goats fed in confinement: 0-day withdrawal period for goats fed Monovet® 90 as a Type C medicated feed containing 20 g monensin/ton

- Milk Discard Time
  - Lactating dairy cows: 0-day milk discard time for lactating dairy cows fed Monovet® 90 as a total mixed ration Type C medicated feed containing 11 to 22 g monensin/ton
  - Lactating dairy cows: 0-day milk discard time for lactating dairy cows fed Monovet® 90 as a component Type C medicated feed containing 11 to 400 g monensin/ton at a rate of 185 to 660 mg monensin/head/day

The studies that supported these withdrawal periods and milk discard times are described as follows.

1. **Title:** A Tissue Residue Study of Monensin in Cattle (Study Number: 011-01208)

   Study Dates: April 18, 2012 to March 21, 2013

   Study Locations:
   In-life phase: Las Cruces, NM, USA
   Analytical phase: Fort Collins, CO, USA

   Study Design:

   Objective: The objective of the study was to compare the concentration of monensin residues in liver tissues from cattle treated with Monovet® 90 (monensin Type A medicated article) or Rumensin™ 90 (monensin Type A medicated article).

   Study Animals: Twenty-eight crossbred cattle (14 males and 14 females), weighing 808 lb. to 1,193 lb., were used in this study.

   Experimental Design: Cattle were assigned to one of three groups. Group 1 consisted of two males and two females fed unmedicated feed. Group 2 consisted of six males and six females fed a Type C medicated feed containing Rumensin™ 90. Group 3 consisted of six males and six females fed a Type C medicated feed containing Monovet® 90.

   Drug Administration: Cattle in Group 1 were fed unmedicated feed for 14 consecutive days. Cattle in Group 2 were fed a Type C medicated feed containing 40 g monensin/ton from Rumensin™ 90 for 14 consecutive days. Cattle in Group 3 were fed a Type C medicated feed containing 40 g monensin/ton from Monovet® 90 for 14 consecutive days.

   Measurements and Observations: On Day 14, cattle were withdrawn from their respective treatment feeds and slaughtered within 12 hours of feed removal. Liver samples were collected and assayed for monensin residues by a validated thin-layer chromatography (TLC) bioautography method. The method's limit of quantification (LOQ) was 0.04 ppm.

   Results: None of the liver samples contained quantifiable concentrations of monensin residues.

   Conclusion: The data from Study 011-01208 indicate that Monovet® 90 is as safe as the RLNAD with respect to monensin residues in edible cattle tissues. Therefore, the data support assigning Monovet® 90 the withdrawal period previously assigned to the RLNAD for beef cattle: 0-day withdrawal period.

2. **Title:** A Study of Monensin Residues in Milk and Liver Tissue from Lactating Dairy Cattle (Study Number: HUV-MN-RS-CD-17-010)

   Study Dates: January 22, 2018, to June 28, 2018

Study Locations:

In-life phase: Tulare, CA, USA
Analytical phase (liver): Fort Collins, CO, USA
Analytical phase (milk): Greenfield, IN, USA

Study Design:

Objective: The objective of the study was to compare the concentration of monensin residues in liver tissues and milk from lactating dairy cows treated with Monovet® 90 (monensin Type A medicated article) or Rumensin™ 90 (monensin Type A medicated article).

Study Animals: Thirty, third parity Holstein cows, weighing 1,462 lb. to 1,921 lb., were used in this study. Cows were pregnant and in mid lactation.

Experimental Design: Cows were assigned to one of three groups. The unmedicated group consisted of two cows fed unmedicated feed. Treatment Group O consisted of 14 cows fed a Type C medicated feed containing Rumensin™ 90. Treatment Group X consisted of 14 cows fed a Type C medicated feed containing Monovet® 90.

Drug Administration: Treatment began on Day 0. Cows in the unmedicated group were fed unmedicated feed for 15 consecutive days. Cows in Treatment Group O were fed 3.5 lb. of a Type C medicated component feed containing 400 g monensin/ton from Rumensin™ 90 each day for 15 consecutive days (700 mg/head/day). Cows in Treatment Group X were fed 3.5 lb. of a Type C medicated component feed containing 400 g monensin/ton from Monovet® 90 each day for 15 consecutive days (700 mg/head/day).

Measurements and Observations: Milk samples were collected during the second milking on Days 11, 12, and 13. Milk samples were assayed for monensin concentrations by a validated LC-MS/MS method. The LC-MS/MS method's limit of detection (LOD) was 0.08 ppb, and the LOQ was 0.24 ppb.

On Day 14, cattle were withdrawn from their respective treatment feeds and slaughtered within 12 hours of medicated feed removal. Liver samples were collected and assayed for monensin residues by a validated TLC bioautography method. The TLC bioautography method's LOQ was 0.04 ppm.

Statistical Method: Because only one milk sample from each treatment group and no liver samples from either treatment group contained quantifiable monensin residue concentrations a Chi-Square Test for Independence was conducted. The Chi-Square Test for Independence determined if the frequency of a cow producing a milk sample testing greater than the method LOD depended on the treatment (α = 0.05). Two cows from Treatment Group O were excluded from the analysis because one was fed the incorrect treatment on Day 12 and the other exhibited depressed feed intake.

Results: The frequency of cows producing a milk sample containing monensin concentrations greater than the method LOD and the results of the Chi-Square Test for Independence are reported in Table III.1.

Table III.1. Frequency of producing a milk sample with monensin concentrations that tested greater than the limit of detection in cows fed a nominal 700 mg monensin *per* head *per* day for 15 consecutive days as a Type C component feed containing either Monovet® 90 (Treatment X) or Rumensin™ 90 (Treatment O)

Period	Treatment X, Number of Cows	Treatment O, Number of Cows	Chi-Square p-value
Day 11	6 of 14	6 of 12	0.7157
Day 12	8 of 14	3 of 12	0.0982
Day 13	7 of 14	6 of 12	1.0000
At Least One Sample on Days 11 to 13	8 of 14	7 of 12	0.9512

Conclusion: The results of the Chi-Square Tests for Independence indicate that the frequency of a cow producing a milk sample that tested positive for monensin concentrations greater than the LOD did not depend on whether cows were treated with Monovet® 90 or Rumensin™ 90. In addition, liver samples from both treatment groups contained non-quantifiable monensin residues. The data from HUV-MN-RS-CD-17-010 indicate that Monovet® 90 is as safe as the RLNAD with respect to monensin residues in edible cattle tissues and milk. Therefore, the data support assigning Monovet® 90 the withdrawal period and milk discard time previously assigned to the RLNAD for lactating dairy cows: 0-day withdrawal period and 0-day milk discard time.

3. Title: Determination of Monensin Residues in Liver Tissue of Angora Goats Following Feeding of Monensin at Levels of 20 and 30 Grams *per* Ton (Study Number: S-AAC-84-01)

Study Dates: October 24, 1983 to April 16, 1984

Study Locations:

In-life phase: San Angelo, TX, USA
Analytical phase: Greenfield, IN, USA

Study Design:

Objective: The objective of the study was to determine the concentration of monensin residues in liver tissues from goats fed a Type C medicated feed containing 20 or 30 g monensin/ton.

Study Animals: Thirty male Angora goats were used in this study.

Experimental Design: Goats were assigned to one of three groups. Group 1 consisted of six goats fed unmedicated feed. Group 2 consisted of 12 goats fed a Type C medicated feed containing 20 g monensin/ton. Group 3 consisted of 12 goats fed a Type C medicated feed containing 30 g monensin/ton.

Drug Administration: Goats were fed their respective treatment feeds for 56 days.

Measurements and Observations: On Day 56, at 0-day withdrawal, six goats were selected from each group and slaughtered. The remaining goats were fed an unmedicated feed for five additional days. At 5 days withdrawn from medicated feed, the remaining 12 goats from Group 2 and Group 3 were slaughtered. After slaughter, liver samples were collected and assayed for monensin residues by a validated TLC bioautography method. The TLC bioautography method's LOQ was 0.04 ppm.

Results: Only one liver sample from a goat in Group 3 slaughtered at 0-day withdrawal (30 g monensin/ton) contained quantifiable monensin residues (0.042 ppm).

Conclusion: Study S-AAC-84-01 originally was submitted to Public Master File (PMF) 5055 to support the approval of the RLNAD in goats. Therefore, it is publicly available for reference to support the approval of other monensin products if information demonstrates similarities between the two monensin products.

The previously described comparative residue studies in beef cattle (Study 011-01208) and lactating dairy cows (HUV-MN-RS-CD-17-010) and the *in vitro* dissolution testing described in Section II (BIOEQUIVALENCE) provide evidence that Monovet® 90 is similar to the RLNAD from a physicochemical and tissue-residue perspective. Therefore, the results from Study S-AAC-84-01 are applicable to Monovet® 90.

The data from Study S-AAC-84-01 support assigning Monovet® 90 the withdrawal period previously assigned to the RLNAD for goats: 0-day withdrawal period.

C. Analytical Method for Residues

The validated analytical method for analysis of residues of monensin in edible cattle and goat tissues is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information Summary request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

An analytical method for analysis of residues of monensin in milk is not required.

IV. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Monovet® 90:

Not for human use. When mixing and handling Monovet® 90, use protective clothing, impervious gloves and a dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse with water.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that Monovet® 90, when used according to the label, is safe and effective.

Additionally, data demonstrate that residues in food products derived from species treated with Monovet® 90 will not represent a public health concern when the product is used according to the label.

VI. APPENDIX

On January 10, 2020, Section II.B.14, which describes the statistical analysis performed in the clinical end-point bioequivalence study, was revised to:

"The bioequivalence of Monovet® 90 and the RLNAD was evaluated using a 90% confidence interval constructed about the ratio of the mean for Monovet® 90 divided by the mean for the RLNAD."

The original text was:

"The bioequivalence of Monovet® 90 and the RLNAD was evaluated using a 90% confidence interval constructed about the ratio of the mean for Monovet® 90 divided by the mean for Monovet® 90."