Date of Approval: August 26, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-783

Coxidin® 90

(monensin Type A medicated article)

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

Broiler Chickens, Laying Hen Replacement Chickens, Layer Breeder Replacement Chickens, Growing Turkeys, and Growing Bobwhite Quail

Broiler and Laying Hen Replacement Chicken and Layer Breeder Replacement Chicken: As an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima*.

Turkeys: For the prevention of coccidiosis in turkeys caused by *Eimeria adenoeides, E. meleagrimitis* and *E. gallopavonis*.

Quail: For the prevention of coccidiosis in growing Bobwhite quail caused by *Eimeria dispersa* and *E. lettyae*.

Sponsored by:

Huvepharma EOOD

Executive Summary

Coxidin® 90 (monensin Type A medicated article) is approved as an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima* in broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens; for the prevention of coccidiosis in turkeys caused by *Eimeria adenoeides, E. meleagrimitis* and *E. gallopavonis*; and for the prevention of coccidiosis in growing Bobwhite quail caused by *Eimeria dispersa* and *E. lettyae*. The reference listed new animal drug (RLNAD) is Coban™ 90 (monensin Type A medicated article) sponsored by Elanco US Inc., under New Animal Drug Application (NADA) 038-878 and NADA 130-736. This is the first generic monensin Type A medicated article for poultry.

Bioequivalence

Monensin is a locally active, poorly soluble drug which is not systemically absorbed, so the sponsor demonstrated that Coxidin® 90 is bioequivalent to Coban™ 90 using a three-pronged, weight-of-evidence approach based on the following:

1) A comparison of product similarity that showed that Coxidin® 90 has qualitative, quantitative, and physiochemical sameness as Coban™ 90; therefore, the drugs are compositionally and structurally equivalent.

2) Two *in vivo* clinical endpoint studies that showed that when used in the manufacture of Type C medicated feeds, the monensin in Coxidin® 90 is available at a similar rate and extent in the gastrointestinal tract of poultry as the monensin in Coban™ 90.

   The sponsor conducted one *in vivo* clinical endpoint study evaluating coccidiosis-induced cecal lesions in broiler chickens. *E. tenella*-challenged chickens receiving Coxidin® 90-medicated feed or Coban™ 90-medicated feed had similar cecal lesion scores, which were less severe than those receiving non-medicated feed. Therefore, Coxidin® 90 was found to be bioequivalent to Coban™ 90 in the prevention of coccidiosis caused by *E. tenella*.

   The sponsor also conducted one *in vivo* clinical endpoint study evaluating coccidiosis in growing turkeys. The clinical endpoint was average daily weight gain (ADWG) following inoculation with *E. gallopavonis*. The ADWG was lowest in *E. gallopavonis*-challenged turkeys that received non-medicated feed. Turkeys that received Coxidin® 90-medicated feed had a similar ADWG as turkeys that received Coban™ 90-medicated feed. Therefore, Coxidin® 90 was found to be bioequivalent to Coban™ 90 in the prevention of coccidiosis caused by *E. gallopavonis*.

3) A comparative *in vitro* dissolution study that showed that Coxidin® 90 and Coban™ 90 have similar dissolution profiles. Because monensin is locally acting within the gastrointestinal tract, dissolution is the critical characteristic that impacts the availability of the drug at its site of action. Both drugs released monensin at the same rate and extent across a range of *in vitro* conditions that mimicked the conditions of the gastrointestinal tract of chickens and turkeys.

The cumulative data described above demonstrate that Coxidin® 90 is bioequivalent to Coban™ 90 in chickens and turkeys. For minor species, such as quail, the Food, Drug, and Administration (FDA) relies on data from biologically similar major species to demonstrate bioequivalence. Quail are very similar to chickens and turkeys; therefore, FDA concluded that Coxidin® 90 is also bioequivalent to Coban™ 90 in quail.

Human Food Safety

Under the NADAs for Coban™ 90, FDA previously established the acceptable daily intake and tolerances for monensin residues, and these values also apply to Coxidin® 90. A tolerance is not required for monensin in the edible tissues (excluding eggs) of chickens, turkeys, and quail.

The data from the three tissue residue studies provided by the sponsor support assigning Coxidin® 90 the withdrawal period previously established for the RLNAD, Coban™ 90. Therefore, a 0-day withdrawal period has been assigned to broiler chickens, laying hen replacement chickens, layer breeder replacement chickens, growing turkeys, and growing Bobwhite quail fed Coxidin® 90 as a Type C medicated feed.

FDA determined that there is a reasonable certainty of no harm for residues of monensin in the edible tissues (excluding eggs) of treated broiler chickens, laying hen replacement chickens, layer breeder replacement chickens, growing turkeys, and growing Bobwhite quail when Coxidin® 90 is used according to the labeling.

Conclusions

Based on the data submitted by the sponsor for the approval of Coxidin® 90, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-783

B. Sponsor

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

Drug Labeler Code: 016592

U.S. Agent Name and Address:

Kelly Beers, Ph.D.
Huvepharma, Inc.
525 West Park Drive
Peachtree City, GA 30269

C. Proprietary Name

Coxidin® 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 C medicated feeds

G. Amount of Active Ingredient

90.7 g/lb

H. How Supplied

25 kg (55.12 lb) bag

I. Dispensing Status

Over the counter (OTC)

J. Dosage Regimen

Broiler Chickens, Laying Hen Replacement Chickens, and Layer Breeder Replacement Chickens: Feed complete feed (90 to 110 g/ton) continuously as the sole ration.

Growing Turkeys: Feed complete feed (54 to 90 g/ton) continuously as the sole ration. The optimum level depends upon the severity of coccidiosis exposure.

Growing Bobwhite Quail: Feed complete feed (73 g/ton) continuously as the sole ration.

K. Route of Administration

Oral

L. Species/Classes

Broiler chickens, laying hen replacement chickens, layer breeder replacement chickens, growing turkeys, and growing Bobwhite quail

M. Indications

Broiler and Laying Hen Replacement Chicken and Layer Breeder Replacement Chicken: As an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati,* and *E. maxima*.

Turkeys: For the prevention of coccidiosis in turkeys caused by *Eimeria adenoeides, E. meleagrimitis* and *E. gallopavonis*.

Quail: For the prevention of coccidiosis in growing Bobwhite quail caused by *Eimeria dispersa* and *E. lettyae.*

N. Reference Listed New Animal Drug

Coban™ 90; monensin Type A medicated article; NADA 038-878 and NADA 130-736; 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 (RLNAD). 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 endpoint study in a food-producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

Coxidin® 90 was determined to be bioequivalent to the RLNAD (Coban™ 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 Coxidin® 90 to show that the generic product is compositionally and structurally equivalent 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 Coxidin® 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 Coxidin® 90 Type A medicated article to the RLNAD, data were provided to confirm that the generic 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. Coxidin® 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. Coxidin® 90 is considered qualitatively (Q1) and quantitatively (Q2) equivalent to the RLNAD.

2. Coxidin® 90 and the RLNAD were determined to be physiochemically (Q3) equivalent based on acceptable comparative characterization of three batches of Coxidin® 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 Coxidin® 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.

[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.

b. Impurities were assessed in extracts of the generic and RLNAD drug products and the monensin API for the generic. Impurity levels in the generic 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 through 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 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 Coxidin® 90 is qualitatively (Q1), quantitatively (Q2), and physiochemically (Q3) equivalent to the RLNAD.

B. Clinical Endpoint Bioequivalence Studies:

To support bioequivalence when a Type A medicated article contains an API whose effect site is locally acting within the gastrointestinal tract, a clinical endpoint 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 endpoint study should be conducted for each species for which the RLNAD is approved with the exception of minor species. Further, the purpose of a clinical endpoint 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 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 in chickens and turkeys. For this approval, two *in vivo* clinical endpoint studies were conducted to demonstrate bioequivalence between the generic and RLNAD products. One clinical endpoint study was conducted to evaluate lesion scores in chickens artificially infected with coccidiosis and the other clinical endpoint study was conducted to evaluate ADWG in turkeys artificially induced with coccidiosis.

1. Clinical Endpoint Bioequivalence Study in Chickens:

Title: A Clinical Endpoint Bioequivalence Study of Monensin on Lesion Scores in Chickens Artificially Induced with Coccidiosis. (Study No. MN-BCPF-1908)

Study Dates: February 14, 2020 to June 11, 2020

Study Location:

In-life phase:	Tulare, CA
Bioanalytical testing:	Greenfield, IN

Study Design:

Objective: The objective of this study was to demonstrate bioequivalence between the generic monensin Type A medicated article and the RLNAD based on a clinical endpoint comparison of lesion scores.

Study Animals: Six hundred normal, healthy, 12-day-old intact, meat-type Cobb 500 male broiler chickens (*Gallus gallus domesticus*) were enrolled in the study. On the day of inoculation, the chickens weighed between 258 and 555 g.

Experimental Design: A randomized, masked, single sequence (parallel) study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies. The study involved 4 treatment groups fed either nonmedicated feed or Type C medicated feed throughout the treatment phase (days -2 to 6) of the study. On day 0, one treatment group was sham inoculated with water and three treatment groups were inoculated with *E. tenella*. The treatment groups were the following:

- non-medicated feed, non-inoculated control group (group 1)
- non-medicated feed, inoculated group (group 2)
- RLNAD medicated feed, inoculated group (group 3)
- generic medicated feed, inoculated group (group 4)

Animals were randomized to cages. Treatment group 1 was housed in 15 cages and treatment groups 2, 3, and 4 were housed in 20 cages. Each cage contained 8 animals. Cages on the top row of each battery were assigned to group 1, and then groups 2, 3, and 4 were randomized to cages within each of rows 2 to 4 using a block randomization design. Each row was a block.

Drug Administration: Each animal received *ad libitum* feed according to their randomized treatment group. Groups 1 and 2 received non-medicated feed. Group 3 was fed the RLNAD Type C medicated feed containing 90 g monensin/ton. Group 4 was fed the generic Type C medicated feed containing 90 g monensin/ton.

Table II.1. Summary of Treatment Groups

Group	Total Cages	Birds per Cage	Total Birds	Type C Feed	Dose	Treatment Days	Inoculation
1	15	8	120	Non-medicated	None	-2 to 6	None
2	20	8	160	Non-medicated	None	-2 to 6	*Eimeria tenella*
3	20	8	160	RLNAD	90 g/ton	-2 to 6	*Eimeria tenella*
4	20	8	160	Generic	90 g/ton	-2 to 6	*Eimeria tenella*

Measurements and Observations: Measurements during the study consisted of body weight, lesion scores, and mortality. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

Cage was the experimental unit. The original lesion scores were transformed to reversed lesion scores for data analysis, as shown below.

Table II.2. Lesion Score Descriptions

Original Lesion Scores	Reversed Lesion Scores	Description
0	4	No gross lesions.
1	3	Very few scattered petechiae on the cecal wall, no thickening of the cecal walls, normal cecal contents present.
2	2	Lesions more numerous with noticeable blood in the cecal contents; cecal wall is somewhat thickened, normal cecal contents present.
3	1	Large amounts of blood or cecal cores present; cecal walls greatly thickened; little, if any, fecal contents in the ceca.
4	0	Cecal wall greatly distended with blood or large caseous cores, fecal debris lacking or included in cores.

To assess the adequacy of the coccidia infection (virulence), ADWG and reversed average lesion scores (reversed ALS) were compared between groups 1 and 2 using a t-test. Mortality rate between groups 1 and 2 was compared using an appropriate non-parametric test. A two-sided test at alpha=0.05 was used for all analyses. The infection was considered adequate if there were statistically significant and clinically relevant differences in lesion scores, ADWG, and mortality rate between the non-medicated/non-infected and non-medicated/infected groups.

To assess the performance of each medicated feed group (group 3 and group 4) compared to group 2, only data from groups 2, 3, and 4 were included in the analyses of ALS, mortality rate, and ADWG. Analyses of variance (ANOVA) were conducted for ADWG and reversed ALS, and mortality rate was analyzed with a generalized linear model. The statistical model for all analyses included treatment as a fixed effect and block as a random effect. The following comparisons were made between groups.

- Group 2 vs. group 3: This represented the performance of the RLNAD to prevent coccidiosis under coccidial disease conditions. A two-sided test at alpha=0.05 was used.
- Group 2 vs. group 4: This represented the performance of the generic to prevent coccidiosis under coccidial disease conditions. A two-sided test at alpha=0.05 was used.

To assess the bioequivalence of the generic test article (T) and RLNAD (R), the 90% confidence interval (CI) for the ratio of means of reversed ALS (T/R) was calculated using Fieller's theorem.

Results:

The adequacy of the *E. tenella* challenge and the performance of the generic and the RLNAD were demonstrated for all three variables: ADWG, reversed ALS and mortality rate.

As seen in Table II.3. below, the ratio of the Least Square (LS) Means for the reversed ALS of the generic to the RLNAD was 0.99 and the 90% CI was (0.90, 1.09), which was contained within the acceptance limits (0.80, 1.25). Therefore, bioequivalence between the generic article and RLNAD was established.

Table II.3. Bioequivalence Evaluation

Variable	Generic LS Mean	RLNAD LS Mean	Ratio◊	Lower 90% CI	Upper 90% CI
Reversed ALS	2.19	2.21	0.99	0.90	1.09

◊ Ratio = Generic/RLNAD

Adverse Reactions:

No adverse reactions were reported in this study.

Conclusions:

The clinical endpoint bioequivalence study demonstrated that monensin in the generic article is available at a similar rate and extent at its site of action in chickens as that of the RLNAD. The ratio of reversed ALS LS means of the generic to the RLNAD was 0.99 and the 90% CI of the ratio was (0.90, 1.09), which was contained within bioequivalence acceptance limits (0.80, 1.25). The bioequivalence for the claim of prevention of coccidiosis due to *E. tenella* in chickens between the generic and RLNAD was established.

2. Clinical Endpoint Bioequivalence Study in Turkeys:

Title: A Clinical Endpoint Bioequivalence Study of Monensin on Weight Gain in Turkeys Artificially Induced with Coccidiosis. (Study No. MN-BCTG-1902)

Study Dates: September 26, 2019 to October 16, 2019

Study Location:

In-life phase: Tulare, CA

Bioanalytical testing: New Orleans, LA

Study Design:

Objective: The objective of this study was to demonstrate bioequivalence between the generic monensin Type A medicated article and the RLNAD based on a clinical endpoint comparison of ADWG.

Study Animals: Four hundred and eighty normal, healthy, 12-day-old, intact, meat-type Nicholas male turkeys were enrolled in the study. On the day of inoculation, turkeys weighted between 130 and 362 g.

Experimental Design: A randomized, masked, single sequence (parallel) study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies. The study involved 4 treatment groups fed either non-medicated feed or Type C medicated feed throughout the treatment phase (days -2 to 6) of the study. On day 0, one treatment group was sham inoculated with water and three treatment groups were inoculated with *E. gallopavonis*. The treatment groups were the following:

- the non-inoculated non-medicated group (group 1)
- the non-medicated inoculated group (group 2)
- the inoculated RLNAD medicated group (group 3)
- the inoculated generic medicated group (group 4)

Animals were randomized to cages. Each treatment group was housed in 15 cages containing 8 animals each. Cages on the top row of each battery were assigned to group 1, and then groups 2, 3, and 4 were randomized to cages within each of rows 2 to 4 using a block randomization design. Each row was a block.

Drug Administration: Each animal received *ad libitum* feed according to their randomized treatment group. Groups 1 and 2 received non-medicated feed. Group 3 was fed the RLNAD Type C medicated feed containing 54 g monensin/ton. Group 4 was fed the generic Type C medicated feed containing 54 g monensin/ton.

Table II.4. Summary of Treatment Groups

Group	Total Cages	Birds per cage	Total Birds	Type C Feed	Dose	Treatment Days	Inoculation
1	15	8	120	Non-medicated	None	-2 to 6	None
2	15	8	120	Non-medicated	None	-2 to 6	*Eimeria gallopavonis*
3	15	8	120	RLNAD medicated	54 g/ton	-2 to 6	*Eimeria gallopavonis*
4	15	8	120	Generic medicated	54 g/ton	-2 to 6	*Eimeria gallopavonis*

Measurements and Observations: Measurements during the study consisted of body weight, fecal scores, and mortality. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

Cage was the experimental unit. To assess the adequacy of the coccidia infection (virulence), ADWG was compared between groups 1 and 2 using a t-test; mortality rate from all causes was compared using a logistic regression, and fecal scores were compared using an appropriate non-parametric test. A two-sided test at alpha=0.05 was used for all analyses. The infection was considered adequate if there were statistically significant and clinically relevant differences in fecal scores, body weight, and mortality rate between the non-medicated/non-infected and non-medicated/infected groups.

To assess the performance of each medicated feed group (group 3 and group 4) compared to group 2, only data from groups 2, 3, and 4 were included in the analyses of ADWG, fecal scores, and mortality rate. An analysis of variance (ANOVA) for ADWG was conducted with group as a fixed effect and block as a random effect. Fecal scores and mortality rate were analyzed using appropriate non-parametric tests.

To assess the bioequivalence of the generic test article (T) and RLNAD (R), the 90% CI for the ratio of means of the ADWG (T/R) was calculated using Fieller's theorem, where the LS means were obtained from the above ANOVA model.

Results:

The adequacy of the *E. gallopavonis* challenge and the effectiveness of the generic and the RLNAD were demonstrated for all three variables: ADWG, fecal scores, and mortality rate.

As seen in Table II.5. below, the ratio of the LS Means for ADWG of the generic to the RLNAD was 1.04 and the 90% CI was (0.97, 1.06), which was contained within the acceptance limits (0.80, 1.25). Therefore, bioequivalence between the generic and RLNAD was established.

Table II.5. Bioequivalence Evaluation

Variable	Generic LS Mean	RLNAD LS Mean	Ratio◊	Lower 90% CI	Upper 90% CI
ADWG	28.63	27.62	1.04	0.97	1.06

◊ Ratio = Generic/RLNAD

Adverse Reactions:

No adverse reactions were reported in this study.

Conclusions:

The clinical endpoint bioequivalence study demonstrated that monensin in the generic article is available at a similar rate and extent at its site of action in turkeys as that of the RLNAD. The ratio of ADWG LS means of the generic to the RLNAD was 1.04 and the 90% CI was (0.97, 1.06), which was contained within

bioequivalence acceptance limits (0.80, 1.25). Bioequivalence for prevention of coccidiosis due to *E. gallopavonis* in turkeys between the generic and 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 Coxidin® 90 across a range of *in vitro* conditions consistent with those encountered in the target species gastrointestinal tract.

Title: Comparative Dissolution of Coxidin® 90 and Coban™ 90 Type A Medicated Articles. (Study No. CD-8.006 R)

Study Dates: June 7, 2019 to March 11, 2021

Study Location: Pazardzhik Province, Bulgaria

Study Design:

Objective: To demonstrate the sameness of the rate and extent of API release of Huvepharma EOOD Coxidin® 90 (monensin Type A medicated article) and Elanco US Inc. Coban™ 90 (monensin Type A medicated article), using comparative *in vitro* dissolution.

Study Standard: Good Laboratory Practices

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

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

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

Table II.6. 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.

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 ($f_2 \geq 50$). 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.

Statistical Methods:

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

Stage 1:

Confirmation that the average percent dissolved versus time profiles are comparable by demonstrating that the f_2' metric[3] is 50 or greater across all conditions under which *in vitro* dissolution was evaluated.

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.

[2] Marylin 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.

[3] The f_2 metric differs from the f_2' metric in that the f_2 metric has variability constraints as documented in the Center for Drug Evaluation and Research (CDER) Dissolution guidance "Dissolution Testing of Immediate Release Solid Oral Dosage Forms", August 1997 which states for the use of the f_2 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 f_2' 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.

Dissolution Comparison Results:

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.7. Results of f_2' used for comparison of dissolution

Test Condition	f_2' Normalized (QA)	f_2' Original Scale (QA)
TC1	---	56.5
TC2	50.4	56.7
TC3	68.4	71.8

QA = monensin A

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 Coxidin® 90 and the RLNAD were plotted graphically and evaluated for each test condition. All dissolution curves for Coxidin® 90 were within the bounds established by the dissolution curves generated for the RLNAD, under identical test conditions.

Table II.8. A summation of the 99% TLs with 95% confidence level (99/95) for test condition 1

Time Point	RLNAD Lower TL – Upper TL (99/95)	Test Article (TA) Coxidin® 90 (mean, n=36) % Dissolution Min – Max	TA values contained in TL Limits?
30 min	14.6 – 38.2	24.8 – 33.0	Yes
60 min	20.8 – 53.3	36.6 – 42.5	Yes
90 min	26.1 – 61.0	44.4 – 50.0	Yes
120 min	30.2 – 66.5	50.5 – 59.0	Yes
240 min	42.0 – 79.6	64.9 – 75.8	Yes
360 min	49.8 – 86.9	72.9 – 84.3	Yes
480 min	54.0 – 92.0	77.5 – 89.2	Yes
600 min	57.9 – 95.5	81.5 – 92.1	Yes

Table II.9. A summation of the 99% TLs with 95% confidence level (99/95) for test condition 2

Time Point	RLNAD Lower TL – Upper TL (99/95)	TA Coxidin® 90 (mean, n=36) % Dissolution Min – Max	TA values contained in TL Limits?
30 min	11.3 – 31.0	20.6 – 27.2	Yes
60 min	17.9 – 41.5	30.9 – 39.2	Yes
90 min	22.3 – 48.8	36.9 – 48.6	Yes
120 min	25.5 – 54.5	43.1 – 53.7	Yes
240 min	34.7 – 67.4	53.2 – 65.7	Yes
360 min	40.6 – 75.6	63.6 – 75.1	Yes
480 min	44.7 – 81.5	63.9 – 78.3	Yes
600 min	47.9 – 85.9	67.7 – 81.4	Yes

Table II.10. A summation of the 99% TLs with 95% confidence level (99/95) for test condition 3

Time Point	RLNAD Lower TL – Upper TL (99/95)	TA Coxidin® 90 (mean, n=36) % Dissolution Min – Max	TA values contained in TL Limits?
30 min	7.6 – 46.3	20.4 – 24.7	Yes
60 min	13.8 – 59.2	30.7 – 37.1	Yes
90 min	18.5 – 67.6	38.1 – 45.8	Yes
120 min	22.5 – 73.5	44.0 – 53.5	Yes
240 min	34.3 – 87.8	59.1 – 68.7	Yes
360 min	44.4 – 93.1	67.5 – 78.2	Yes
480 min	50.9 – 98.6	73.5 – 82.4	Yes
600 min	55.4 – 104.4	77.2 – 87.6	Yes

Conclusion:

Dissolution profiles of 60 samples from five lots of Coban™ 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 Coxidin® 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.

Bioequivalence Conclusion:

The cumulative data supports the bioequivalence between Coxidin® 90 and the RLNAD. Both formulations contain the same active ingredient in the same concentration and dosage form. Further, Coxidin® 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 Coxidin® 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 endpoint bioequivalent study) conditions using an approved indication for the RLNAD in chickens and an approved indication for the RLNAD in turkeys. The proposed product is considered bioequivalent to the RLNAD.

III. HUMAN FOOD SAFETY

A. Acceptable Daily Intake and Tolerances for Residues

The acceptable daily intake (ADI) for total residues of monensin is 12.5 µg/kg of body weight *per* day. The tolerances established for the RLNAD apply to the generic product. A tolerance is not required for monensin in edible tissues (excluding eggs) of chickens, turkeys, and quail, under 21 CFR 556.420.

B. Withdrawal Periods

The Agency evaluated three studies to assign a 0-day withdrawal period for broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens fed Coxidin® 90 as a Type C medicated feed containing 90 to 110 g monensin/ton, growing turkeys fed Coxidin® 90 as a Type C medicated feed containing 54 to 90 g monensin/ton, and for growing Bobwhite quail fed Coxidin® 90 as a Type C medicated feed, containing 73 g monensin/ton.

The studies that supported this withdrawal period are described below.

1. **Title:** A Tissue Residue Study of Monensin Sodium in Chickens. (Study No. HVP-SP-1008, Study No. SBL 011-01199)

   Study Dates: September 30, 2011 to August 23, 2012

   Study Location:

In-life phase:	Las Cruces, NM
Analytical testing:	Fort Collins, CO

   Study Design:

   Objective: The purpose of this study was to demonstrate that monensin residues resulting from chickens fed for 14 days with a Type C medicated feed prepared from the generic Type A medicated article, Coxidin® 90, were similar to residues resulting from chickens fed for 14 days with a Type C medicated feed prepared from the RLNAD, Coban™ 90.

   Study Animals: One hundred forty healthy 1-day old chickens were obtained. The birds were about 4 weeks of age when the 7-day acclimation period began (body weights ranged from 1,013 to 1,662 g).

   Experimental Design: The study was conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies. The 108 chickens selected for the study were randomly assigned to three treatment groups (36 birds (18 males, 18 females) in each group).

Drug Administration: Group 1 chickens were fed unmedicated feed for 14 days. Group 2 chickens were fed a Type C medicated feed containing the RLNAD, Coban™ 90, for 14 days. Group 3 chickens were fed a Type C medicated feed containing the generic product, Coxidin® 90, for 14 days. The medicated feeds contained 149-194 g monensin/ton.

Measurements and Observations: The chickens in Groups 2 and 3 were slaughtered within 4.5 hours after the medicated feeds were withdrawn. The entire liver and ≥100 g skin with adhering fat were collected from each bird. Monensin residues were measured using a method with thin layer chromatography and bio-autography.

Results: The monensin concentrations in all liver samples were below measurable concentrations (<0.4 ppm). Monensin was detectable in two of the ten composite skin/fat samples from Group 2 (Coban™ 90) and in three samples from Group 3 (Coxidin® 90), but only one of these composites in each group was above the analytical method's limit of quantitation.

Conclusion: The data from Study HVP-SP-1008, SBL 011-01199 indicate that Coxidin® 90 is as safe as the RLNAD with respect to monensin residues in edible chicken tissues. Therefore, the data support assigning Coxidin® 90 the withdrawal period previously assigned to the RLNAD for broiler chickens, laying hen replacement chickens, and layer breeder replacement chickens: 0-day withdrawal period.

2. **Title:** A Tissue Residue Study of Monensin in Turkeys. (Study No. MN-RSTF-2218)

   Study Dates: December 1, 2022 to May 24, 2023

   Study Locations:

In-life phase:	Tulare, CA
Analytical testing:	Fort Collins, CO
Feed Analysis:	Indianapolis, IN

   Study Design:

   Objective: The objective of the study was to compare the concentration of monensin residues in liver and skin with adhering fat tissues from turkeys treated with Coxidin® 90 or Coban™ 90 (monensin Type A medicated article).

   Study Animals: Thirty-eight Nicholas-Select turkey poults (10 males and 28 females), weighing 4.8 kg to 10.3 kg, were used in this study.

   Experimental Design: The study was conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies. Turkeys were assigned to one of three groups. Group 1 consisted of six females fed unmedicated feed. Group 2 consisted of 11 females and five males fed a Type C medicated feed containing Coxidin® 90.

Group 3 consisted of 11 females and five males fed a Type C medicated feed containing Coban™ 90.

Drug Administration: Turkeys in Group 1 were fed unmedicated feed for 14 consecutive days. Turkeys in Group 2 were fed a Type C medicated feed containing 110 g monensin/ton from Coxidin® 90 for 14 consecutive days. Turkeys in Group 3 were fed a Type C medicated feed containing 110 g monensin/ton from Coban™ 90 for 14 consecutive days.

Measurements and Observations: On Day 14, turkeys were withdrawn from their respective treatment feeds and slaughtered within six hours of feed removal. Liver and skin with adhering fat samples were collected and analyzed for monensin by the official thin-layer chromatography (TLC) bioautography method. The primary decisional criterion was the size of the zones of inhibition measured on the TLC bioautograph.

Statistical Method: Because of the limited number of liver samples with detectable monensin residues, a statistical analysis was not performed. The zone sizes were comparable between the two groups.

The zone areas from the skin with adhering fat samples were analyzed using an upper tolerance limit approach. The skin with adhering fat zone area values from Group 3 (Coban™ 90) were confirmed to be normally distributed by the Shapiro-Wilk test ($p = 0.2645$). The 99th percentile upper tolerance limit with 95% confidence for Group 3's (Coban™ 90) skin with adhering fat zone area values was calculated based on the non-central t distribution. The upper tolerance limit was calculated to be 210.58 mm^2. The individual zone areas for Group 2's (Coxidin® 90) skin with adhering fat samples were compared to this upper tolerance limit. None of Group 2's (Coxidin® 90) skin with adhering fat zone areas exceeded the upper tolerance limit for Group 3 (Coban™ 90).

Results: Only two out of 16 liver samples from Group 2 (Coxidin® 90) produced zones of inhibition on the TLC bioautographs, and five out of 16 liver samples from the Group 3 (Coban™ 90) produced zones of inhibition on the TLC autobiographs. For skin with adhering fat samples, all samples from both groups produced zones of inhibition on the TLC bioautographs. Mean and standard deviation values for zone of inhibition areas are presented in Table III.1.

Table III.1. Mean and standard deviation (SD) values for zone of inhibition areas produced on the thin-layer autobiograph for liver and skin with adhering fat samples obtained from chickens fed either a Type C medicated feed containing Coxidin® 90 (Group 2) or a Type C medicated feed containing Coban™ 90 (Group 3)

Tissue	Group 2 Zone Area, mm^2 (mean ± SD)	Group 3 Zone Area, mm^2 (mean ± SD)
Liver	53.7 ± 20.1 (n = 2)	51.8 ± 17.8 (n = 5)
Skin with Adhering Fat	59.6 ± 33.8 (n = 16)	57.5 ± 44.2 (n = 16)

Conclusion: The data from Study MN-RSTF-2218 indicate that Coxidin® 90 is as safe as the RLNAD with respect to monensin residues in edible turkey tissues. Therefore, the data support assigning Coxidin® 90 the withdrawal period previously assigned to the RLNAD for growing turkeys: 0-day withdrawal period.

3. **Title:** Tissue Residue Depletion Study in Quail.

   Study Dates: May 26, 1985 to July 20, 1985

   Study Locations:

   In-life phase: Beltsville, MD

   Analytical testing: Greenfield, IN

   Study Design:

   Objective: The objective of the study was to determine the concentration of monensin residues in liver tissues from quail fed a Type C medicated feed containing 73 g monensin/ton.

   Study Animals: Sixty quail were used in this study.

   Experimental Design: Quail were assigned to one of two groups. Group 1 consisted of thirty quail fed unmedicated feed. Group 2 consisted of thirty quail fed a Type C medicated feed containing 73 g monensin/ton.

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

   Measurements and Observations: On Day 56, at 0-day withdrawal, quail in Groups 1 and 2 were slaughtered. After slaughter, liver samples were collected and assayed for monensin residues by the official TLC bioautography method. The TLC bioautography method's limit of quantification was 0.04 ppm.

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

   Conclusion: This study originally was submitted to Public Master File (PMF) 5014 to support the approval of the RLNAD in Bobwhite quail. 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 chickens (Study HVP-SP-1008, SBL 011-01199) and turkeys (Study MN-RSTF-2218) and the clinical endpoint and *in vitro* dissolution testing described in Section II (BIOEQUIVALENCE) provide a weight of evidence that Coxidin® 90 is similar to the RLNAD from a physicochemical and tissue-residue perspective. Therefore, the results from the tissue residue depletion study in quail are applicable to Coxidin® 90.

The data from the tissue residue depletion study in quail from PMF 5014 support assigning Coxidin® 90 the withdrawal period previously assigned to the RLNAD for growing Bobwhite quail: 0-day withdrawal period.

C. Analytical Method for Residues

The validated analytical method for analysis of residues of monensin 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 request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

IV. USER SAFETY

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

NOT FOR HUMAN USE

User Safety Warning: When mixing and handling Coxidin® 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 thoroughly with water.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that Coxidin® 90, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

Additionally, data demonstrate that residues in food products derived from broiler chickens, laying hen replacement chickens, layer breeder replacement chickens, growing turkeys, and growing Bobwhite quail treated with Coxidin® 90 will not represent a public health concern when the product is used according to the label.