Date of Approval: May 21, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-514

Experior™ and Rumensin™

(lubabegron Type A medicated article) and (monensin Type A medicated article)

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

Beef steers and heifers fed in confinement for slaughter

Original approval of an Animal Drug Availability Act of 1996 (ADAA) feed combination for the indications listed in Section I.L.

Sponsored by:

Elanco US Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-514

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Names

Experior™ and Rumensin™

D. Drug Product Established Names

Lubabegron Type A medicated article and monensin Type A medicated article

E. Pharmacological Categories

Experior™: beta-adrenergic agonist/antagonist
Rumensin™: anticoccidial

F. Dosage Form

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

G. Amount of Active Ingredients in Currently Marketed Products[1]

Experior™: 10 g/kg (4.54 g/lb)
Rumensin™: 90.7 g/lb

H. How Supplied

Experior™: 10 kg bags
Rumensin™: 25 and 600 kg bags

I. Dispensing Status

OTC

J. Route of Administration

Oral

[1] The sponsor of these individual currently marketed Type A medicated articles may have approvals for other strengths that are for use in the same species and class, for the same indications, and at the same dosages, but are not currently marketing those strengths of these Type A medicated articles. Such strengths, when legally marketed, are also approved for use in the manufacture of Type C medicated feeds that are the subject of this approval.

K. Species/Classes

Beef steers and heifers fed in confinement for slaughter

L. Indications and Dosage Regimens

1. For reduction of ammonia gas emissions per pound of live weight and hot carcass weight and prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.

    a. 1.25 to 4.54 g/ton to provide 13 to 90 mg/hd/day of Experior™ for reduction of ammonia gas emissions per pound of live weight and hot carcass weight

    b. 10 to 40 g/ton to provide 0.14 to 0.42 mg/lb body weight per day, depending upon severity of coccidiosis challenge, up to 480 mg/hd/day, of Rumensin™ for prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*

    Feed continuously as sole ration during the last 14 to 91 days on feed.

2. For reduction of ammonia gas emissions per pound of live weight and hot carcass weight and improved feed efficiency in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.

    a. 1.25 to 4.54 g/ton to provide 13 to 90 mg/hd/day of Experior™ for reduction of ammonia gas emissions per pound of live weight and hot carcass weight

    b. 5 to 40 g/ton to provide 50 to 480 mg/hd/day of Rumensin™ for improved feed efficiency

    Feed continuously as sole ration during the last 14 to 91 days on feed.

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the ADAA of 1996, allows for drugs to be fed in combination in or on medicated feed without additional demonstration of their effectiveness or target animal safety when certain conditions are met. In those cases, the FD&C Act provides that effectiveness and target animal safety of each drug, demonstrated in its NADA at the time of the approval, are adequate. The Agency has based its determination of the effectiveness and target animal safety of the combination of lubabegron Type A medicated article and monensin Type A medicated article on the effectiveness and target animal safety of the previously separately approved conditions of use for Experior™ and Rumensin™ for use in beef steers and heifers fed in confinement for slaughter, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness;

- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population;
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness;
- there was not a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that was not adequately evaluated based on the information contained in the application for the combination, and no data presented in the application raised a safety concern with the Agency; and
- there was not a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and no data presented in the application raised a safety concern with the Agency.

Effectiveness and target animal safety of the individual drugs in this combination product has been established by data in the following NADAs (see Table II.1):

Table II.1. Summary of effectiveness and target animal safety for the individual drugs subject to this combination approval.

Drug Product	Indication(s)	Approval Information
Experior™ Sponsored by Elanco US Inc.	For use in feeds for beef steers and heifers fed in confinement for slaughter for reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.	NADA 141-508 FOI Summary dated November 6, 2018
Rumensin™ Sponsored by Elanco US Inc.	1. For use in feeds for cattle fed in confinement for slaughter for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii.* 2. For use in feeds for cattle fed in confinement for slaughter for improved feed efficiency.	NADA 095-735 21 CFR 558.355

III. HUMAN FOOD SAFETY

The human food safety of each drug was adequately demonstrated in its NADA at the time of the approval. In general, this means that additional microbial food safety and toxicology data were not needed; however, additional residue chemistry data were needed for residue depletion and assay noninterference for the combination product. The Agency has based its determination of the human food safety of the combination

of lubabegron Type A medicated article and monensin Type A medicated article on the human food safety of the previously separately approved conditions of use for Experior™ and Rumensin™ for use in beef steers and heifers fed in confinement for slaughter, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, and
- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Microbial Food Safety

With respect to the human food safety evaluation for these types of combination new animal drug approvals, the Agency evaluates whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs of the combination interferes with the methods of analysis of another active ingredient or drug in the combination [section 512(d)(4)(A) of the FD&C Act]. Therefore, the effects of this combination of Experior™ and Rumensin™ on antimicrobial resistance development among bacteria of public health concern in or on treated beef steers and heifers fed in confinement for slaughter was not assessed.

B. Toxicology

Safety of the individual drugs in this combination product has been established by data in the following NADAs (see Table III.1):

Table III.1. Toxicology assessment of individual drugs in this combination product.

Drug Product	Approval Information
Experior™	NADA 141-508 FOI Summary dated November 06, 2016
Rumensin™	NADA 095-375 FOI Summaries dated December 16, 1998, and September 5, 2013

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      CVM did not require total residue and metabolism studies for this approval. NADA 141-508 (FOI Summary dated November 6, 2018) contains summaries of studies supporting the approval of lubabegron in cattle. NADA 095-375 (as published in the FEDERAL REGISTER (40 FR 58289) on December 16, 1975, and FOI Summary dated October 28, 2004) contains summaries of studies supporting the approval of monensin in cattle.

   b. Comparative Metabolism Studies

      CVM did not require comparative metabolism studies for this approval. NADA 141-508 (FOI Summary dated November 6, 2018) contains summaries of studies supporting the approval of lubabegron in cattle. NADA 095-375 (as published in the FEDERAL REGISTER (40 FR 58289) on December 16, 1975, and FOI Summary dated October 28, 2004) contains summaries of studies supporting the approval of monensin in cattle.

   c. Residue Depletion Studies

      (1) Study Number: 150343

      Study Dates: July 2016 to October 2017

      Study Location: Parma, Idaho

      Study Design:

      Objective: The objective of this GLP study was to demonstrate residue noninterference for lubabegron in combination with monensin and/or melengestrol acetate (MGA) following administration as a Type C medicated feed at a dose of 13 g/ton in the feed. Tissue concentrations of the administered drugs were measured after 0-day withdrawal. Dosing: Forty-two growing cattle weighing from 745-922 lbs. were used for the study. They were randomized to one of five treatment groups as described in Table III.C.1. The two control animals were slaughtered before the acclimation phase. Animals being treated with monensin received the lower dose of monensin (30 g/ton) during a 14-day acclimation phase, and then increased to the higher dose (40 g/ton) during the 15-day treatment phase. Lubabegron and MGA were provided to the animals during both the acclimation and treatment phases. Lubabegron and monensin were provided as a Type C medicated feed while MGA was provided as a top dress.

Table III.2. Treatment Groups

TG	Lubabegron Target Dose (g/ton)	Monensin Target Dose (g/ton)	MGA Target Dose (mg/hd/day)	Treatment Duration (days)	Number of animals*
01	0	0	0	0	1M; 1F
02	13	30/40	0	≥28	5M; 5F
03	13	0	0.5	≥28	10 F
04	13	30/40	0.5	≥28	10 F
05	13	0	0	≥28	5M; 5F

*M = male; F = female

Experimental Design: Cattle were removed from medicated feed approximately 8-10 hours prior to slaughter. Liver tissue was collected from all treatment groups, and omental fat was collected from the control group and groups receiving MGA. Liver tissue was analyzed for the concentration of lubabegron using the official LC-MS/MS method and monensin using and AOAC Final Action LC-MS/MS method. Omental fat tissue was analyzed for the concentration of MGA using the official gas chromatographic method.

Results: The results of analysis of lubabegron, monensin, and MGA are shown in Table III.3 below. Treatment group 02 received the combination of lubabegron and monensin. Residues of monensin in liver were below the tolerance at the 0-day withdrawal period. The mean lubabegron liver concentration was also below the tolerance, but one animal in treatment group 02 had a liver lubabegron concentration above the tolerance. The animals in this study received 13 g/ton lubabegron, a dose that is more than two times higher than the maximum approved dose for lubabegron of 4.54 g/ton.

Table III.3. Mean Residues for Lubabegron, Monensin, and MGA (ppb)

Treatment Group	Lubabegron in Liver (%CV)	Monensin in Liver (%CV)	MGA in Fat (%CV)
02	7.4 (54.3)	18.7 (31.2)	NA
03	4.4 (65.8)	NA	8.1 (18.8)
04	4.0 (42.8)	18.9 (42.8)	8.1 (25.6)
05	6.0 (34.2)	NA	NA

NA: Not Applicable, animals did not receive the treatment

(2) Study Number: 1700188

Study Dates: April 2017 to December 2017

Study Location: Parma, Idaho

Study Design:

Objective: The objective of this GLP study was to demonstrate residue noninterference for lubabegron in combination with monensin, MGA, and/or tylosin following administration as a Type C medicated feed at a dose of 5 g/ton in the feed. Tissue concentrations of the administered drugs were measured after 0-day withdrawal.

Dosing: Thirty-two growing cattle weighing from 534-689 lbs. were used for the study. They were randomized to one of four treatment groups as described in Table III.4. The two control animals were slaughtered before the acclimation phase. Animals being treated with monensin received the lower dose of monensin (30 g/ton) during a 14-day acclimation phase, and then increased to the higher dose (40 g/ton) during the 15-day treatment phase. Lubabegron, tylosin, and MGA were provided to the animals during both the acclimation and treatment phases. Lubabegron, monensin, and tylosin were provided as a Type C medicated feed while MGA was provided as a top dress.

Table III.4. Treatment Groups

Treatment Group	Lubabegron Target Dose (g/ton)	Monensin Target Dose (g/ton)	MGA Target Dose (mg/hd/day)	Tylosin Target Dose (g/ton)	Number of Animals
01	0	0	0	0	1M; 1F
02	5	0	0	0	5M; 5F
03	5	30/40	0	10	10M
04	5	30/40	0.5	10	10F

Experimental Design: Cattle were removed from medicated feed approximately 10-12 hours prior to slaughter. Liver tissue was collected from all treatment groups, and omental fat was collected from the control group and treatment group 04. Liver tissue was analyzed for the concentration of lubabegron using the official LC-MS/MS method, monensin using an AOAC Final Action LC-MS/MS method, and tylosin using the official microbiological method. Omental fat tissue was analyzed for the concentration of MGA using the official gas chromatographic method.

Results: The results of analysis of lubabegron, monensin, and MGA are shown in Table III.5 below. All animals had residues for lubabegron, monensin, and MGA that were below their respective tolerances in all treatment groups. The tylosin analysis found no detectable tylosin residues in any of the samples.

Table III.5. Mean Residues for Lubabegron, Monensin, and MGA (ppb)

Treatment Group	Lubabegron in Liver	Monensin in Liver	MGA in Fat
02	3.3[1]	NA	NA
03	BLOQ	14.9	NA
04	3.4[1]	17.2	10.4

NA: Not applicable, the animals in these groups were not treated with the drug
BLOQ: All samples were below the limit of quantitation (BLOQ) (3.0 ppb).
[1]: Mean of 3 animals, 7 animals were below the LOQ (3.0 ppb).

d. Method Noninterference Studies

(1) Study Number: 8320-464

Study Dates: May 2015 to December 2015

Study Location: Greenfield, IN

Study Design:

Objective: The objective of this GLP study was to demonstrate analytical method noninterference for lubabegron, monensin, tylosin, and MGA in the analytical methods for lubabegron, monensin, and MGA.

Experimental Design: Control cattle liver tissue was fortified with lubabegron, monensin, tylosin, and/or MGA. These samples were then analyzed using the official LC-MS/MS analytical method for lubabegron and the AOAC Final Action LC-MS/MS method for monensin. Control cattle fat tissue was fortified with MGA, lubabegron, monensin, and/or tylosin. These samples were then analyzed using the official gas chromatographic analytical method for MGA.

Results: The results for the analyte in each assay were compared to the appropriate accuracy criteria from VICH GL49. For lubabegron in liver, the mean percent accuracy for all groups was between 88.3-98.5%. For monensin in liver, the mean percent recovery for all groups was between 91.4-94.4%. For MGA in fat, the mean percent recovery for all groups was between 91.6-96.1%. The percent coefficient of variation (%CV) for all groups in all assays was <10%. Lubabegron, monensin, MGA, and tylosin do not interfere with the detection of lubabegron, monensin, and MGA in their respective analytical methods.

2. Target Tissues and Marker Residues

No reassessments for target tissue and marker residue were needed for this approval. The marker residue for lubabegron is parent lubabegron and the

target tissue is liver (NADA 141-508, FOI Summary dated November 6, 2018). Neither a target tissue or a marker residue is codified for monensin.

3. Tolerances

The tolerance for lubabegron (the marker residue) in cattle liver is 10 ppb (NADA 141-508, FOI Summary dated November 6, 2018). Tolerances for monensin in cattle are as follows: 0.10 ppm in liver, 0.05 ppm in muscle, kidney, and fat (21 CFR 556.420, as published in the FEDERAL REGISTER (72 FR 56897) on October 5, 2007).

4. Withdrawal Period and/or Milk Discard Time, and/or Honey Discard Time

Study 150343 showed that residues of monensin were below the 100 ppb tolerance in cattle liver after a 0-day withdrawal period when fed in combination with lubabegron dosed at 13 g/ton. Study 1700188 showed that residues of lubabegron, monensin, and tylosin in cattle liver were all below their respective tolerances after a 0-day withdrawal period when lubabegron was dosed at 4.54 g/ton (the maximum approved dose). The data support assignment of a 0-day withdrawal period for lubabegron dosed at 1.25 to 4.54 g/ton in combination with monensin dosed at 5 to 40 g/ton.

D. Analytical Method for Residues

1. Determinative Method

The LC-MS/MS determinative method for lubabegron in cattle liver is described in NADA 141-508 (FOI Summary dated November 6, 2018). The bioautographic method for determination of monensin in cattle tissues is described in NADA 095-735 (as published in the FEDERAL REGISTER (26 FR 4359) on May 19, 1961). An AOAC Final Action LC-MS/MS method for monensin was bridged to the official bioautographic method and used as indicated above.

2. Confirmatory Method

An LC-MS/MS confirmatory method for lubabegron is described in NADA 141-508 (FOI Summary dated November 6, 2018). A confirmatory method was not required for monensin. However, the AOAC Final Action LC-MS/MS method for monensin was bridged to the official bioautographic method and is capable of confirming monensin in tissue samples.

3. Availability of Method

The validated analytical method for analysis of residues of lubabegron and 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

CVM did not require user safety studies for this approval. The user safety for this combination was established based on evaluation of the individual component drugs under NADA 141-508, 095-375, and 012-491.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type C medicated feed:

User Safety Warning: Not for human use. Keep out of reach of children. The active ingredient in Experior, lubabegron, is a beta-adrenergic agonist/antagonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. When mixing and handling Experior, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water; if wearing contact lenses, rinse eyes first, then remove contact lenses and continue to rinse for 5-20 minutes. If irritation persists, seek medical attention. The safety data sheet contains more detailed occupational safety information. To report adverse drug events, access medical information, or obtain additional product information, call Elanco US Inc. at 1-800-428-4441. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the FD&C Act and 21 CFR part 514. The data contained in the previously approved NADAs for Experior™ and Rumensin™ demonstrate that, when they are used according to the label, they are safe and effective for reduction of ammonia gas emissions per pound of live weight and hot carcass weight, improved feed efficiency, and prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed. Additionally, data demonstrate that residues in food products derived from beef steers and heifers fed in confinement for slaughter administered Experior™ and Rumensin™ will not represent a public health concern when the combination medicated feed is used according to the label.

A. Marketing Status

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.