Date of Approval: May 21, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-512

Experior™ and Rumensin™ and Tylan™

(lubabegron Type A medicated article) and (monensin Type A medicated article) and (tylosin phosphate 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 141-512

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Names

Experior™ and Rumensin™ and Tylan™

D. Drug Product Established Names

Lubabegron Type A medicated article and monensin Type A medicated article and tylosin phosphate Type A medicated article

E. Pharmacological Categories

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

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
Tylan™: 100 g/lb

H. How Supplied

Experior™: 10 kg bags
Rumensin™: 25 and 600 kg bags
Tylan™: 50 lb bags

[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.

I. Dispensing Status

VFD

J. Route of Administration

Oral

K. Species/Class(es)

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, prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*, and reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* 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*

    c. 8 to 10 g/ton to provide 60 to 90 mg/hd/day of Tylan™ for reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes*

    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, improved feed efficiency, and reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* 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

    c. 8 to 10 g/ton to provide 60 to 90 mg/hd/day of Tylan™ for reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes*

    Feed continuously as the 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, monensin Type A medicated article and tylosin phosphate Type A medicated article on the effectiveness and target animal safety of the previously separately approved conditions of use for Experior™, Rumensin™ and Tylan™ 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 have 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 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
Tylan™ Sponsored by Elanco US Inc.	For use in feeds for beef cattle for reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes*.	NADA 012-491 21 CFR 558.625

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, monensin Type A medicated article, and tylosin phosphate Type A medicated article on the human food safety of the previously separately approved conditions of use for Experior™, Rumensin™ and Tylan™ 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™, Rumensin™ and Tylan™ 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
Tylan™	NADA 012-491, NADA 013-076 NADA 012-491 (as published in the FEDERAL REGISTER (26 FR 4359) on May 19, 1961) and NADA 013-076 FOI Summary dated July 30, 2014

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. NADA 012-491 (as published in the FEDERAL REGISTER (26 FR 4359) on May

19, 1961) contains summaries of studies supporting the approval of tylosin 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. NADA 012-491 (as published in the FEDERAL REGISTER (26 FR 4359) on May 19, 1961) contains summaries of studies supporting the approval of tylosin in cattle.

c. Residue Depletion Study

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, melengestrol acetate (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.2. 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.2. Treatment Groups

TG	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

* M = male; F = female

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.3 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.3. 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 (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) Study Number: 033389

Study Dates: May 2015 to October 2015

Study Location: Concord, OH

Study Design**:**

Objective: The objective of this non-GLP study was to demonstrate that lubabegron, monensin, and MGA do not interfere with the microbiological method for determination of tylosin.

Experimental Design: Control cattle liver tissue was fortified with tylosin in combination with lubabegron, monensin, and/or MGA. These samples were then analyzed using the microbiological method for determination of tylosin.

Results: Lubabegron, monensin, and MGA did not have a significant effect on the formation of inhibition zones by tylosin. Lubabegron, monensin, and MGA do not interfere with the determination of tylosin in cattle liver tissue.

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 or tylosin.

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). Tolerances for tylosin in cattle are as follows: 0.2 ppm in uncooked fat, muscle, liver, and kidney (21 CFR 556.740).

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

   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 at 5 to 40 g/ton and tylosin at 8 to 10 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). The microbiological method for determination of tylosin in cattle tissues is described in NADA 012-491 (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). Confirmatory methods were not required for monensin and tylosin. 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, monensin, and tylosin are 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™, Rumensin™, and Tylan™ 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, prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*, and reduction of incidence of liver abscesses associated with *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* 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™, Rumensin™, and Tylan™ will not represent a public health concern when the combination medicated feed is used according to the label.

A. Marketing Status

The decision to restrict this drug to use by or upon a lawful veterinary feed directive issued by a licensed veterinarian was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, and because restricting this drug product to use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product and to slow or prevent any potential for the development of bacterial resistance to antimicrobial drugs.

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.