Date of Approval: October 25, 2024

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-590

MGA® and Experior™ and Rumensin™

(melengestrol acetate Type A medicated article) and (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

Growing beef heifers fed in confinement for slaughter

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

Sponsored by:

Elanco US Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-590

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Names

MGA® and Experior™ and Rumensin™

D. Drug Product Established Names

melengestrol acetate Type A medicated article and lubabegron Type A medicated article and monensin Type A medicated article

E. Pharmacological Categories

MGA®: steroid hormone
Experior™: beta-adrenergic agonist/antagonist
Rumensin™: ionophore

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]

MGA® 200 (dry formulation): 200 mg per lb of melengestrol acetate
MGA® 500 (liquid formulation): 500 mg per lb of melengestrol acetate
Experior™: 10 g per kg (4.54 g per lb) and 50 g per kg (22.7 g per lb) of lubabegron (as lubabegron fumarate)
Rumensin™: 90.7 g per lb of monensin, USP

H. How Supplied

MGA® 200 (dry formulation): 50 lb (22.7 kg) bag
MGA® 500 (liquid formulation): 40 lb (18 kg) container
Experior™: 10 kg (22.04 lb) bag
Rumensin™: 25 kg (55.12 lbs) bag

[1] The sponsors 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

Over-the-counter (OTC)

J. Route of Administration

Oral

K. Species/Class

Growing beef heifers fed in confinement for slaughter

L. Indication and Dosage Regimen

1. For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), for reduction of ammonia gas emissions per pound of live weight and hot carcass weight, and for the prevention and control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii* in growing beef heifers fed in confinement for slaughter during the last 14 to 91 days on feed.

    a. 0.25 to 2 g/ton of melengestrol acetate (as MGA® 200 or MGA® 500) to provide 0.25 to 0.5 mg melengestrol acetate per head per day for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat)

    b. 1.25 to 4.54 g/ton of lubabegron (as lubabegron fumarate) (as Experior™) to provide 13 to 90 mg lubabegron per head per day for reduction of ammonia gas emissions per pound of live weight and hot carcass weight

    c. 10 to 40 g/ton of monensin (as Rumensin™) to provide 0.14 to 0.42 mg monensin per pound of body weight per day, depending upon severity of challenge, up to a maximum of 480 mg monensin per head per day for the prevention and control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii*

    The melengestrol acetate Type C top-dress medicated feed (0.5 to 2 lb(s) per head per day) must be top dressed onto or mixed at feeding with a Type C medicated feed containing lubabegron and monensin. Feed 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 melengestrol acetate Type A medicated article, 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 MGA®, Experior™ and Rumensin™ for use in growing beef heifers fed in

confinement for slaughter during the last 14 to 91 days on feed, 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 has been established by data in the following NADAs (refer to Table II.1):

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

Drug Product	Indications[2]	Approval Information
MGA®* Sponsored by Zoetis Inc.	For use in feeds for heifers fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat).	NADA 039-402[3] (21 CFR 558.342)
Experior™ Sponsored by Elanco US Inc.	For use in feeds for beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed for reduction of ammonia gas emissions per pound of live weight and hot carcass weight.	NADA 141-508 (refer to the FOI Summary, dated November 6, 2018)
Rumensin™ Sponsored by Elanco US Inc.	For use in feeds for growing beef steers and heifers fed in confinement for slaughter for the prevention and control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii*.	NADA 095-735 (21 CFR 558.355)

* Zoetis Inc. has provided Elanco US Inc. right of reference to use MGA® in this combination.

III. HUMAN 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, only additional residue chemistry data and assay noninterference information were needed to support approval of this ADAA feed-use combination. The Agency has based its determination of the human food safety of the combination of melengestrol acetate, lubabegron, and monensin on the human food safety of the previously separately approved conditions of use for MGA®, Experior™ and Rumensin™ for use in growing beef heifers fed in confinement for slaughter during the last 14 to 91 days on feed, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

[2] The target animals listed in this table are as currently listed on the individual drug product medicated article labeling. For the current approval, the target animal terminology reflects current nomenclature as described in Guidance for Industry #191, Appendix III (https://www.fda.gov/media/70423/download).
[3] Zoetis Inc.'s melengestrol acetate Type A medicated article was originally approved under NADA 034-254, and its melengestrol acetate Type A liquid medicated article was originally approved under NADA 039-402. The two files were administratively combined under NADA 039-402 in 2009, and NADA 039-402 contains all information for both the dry and liquid formulations. NADA 034-254 is no longer active.

- 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

As noted, Section 512(d)(4)(A) of the FD&C Act, limits the Center for Veterinary Medicine's (CVM's) human food safety evaluation for these types of ADAA feed-use combination new animal drug approvals; therefore, microbial food safety was not assessed.

B. Toxicology

As noted, Section 512 (d)(4)(A) of the FD&C Act limits CVM's human food safety evaluation for these types of ADAA feed-use combination new animal drug approvals; therefore, toxicology assessment of these types of combination new animal drugs was not performed. Safety of the individual drugs in this combination has been established by data in the following NADAs (refer to Table III.1.):

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

Drug Product	Approval Information
MGA®	NADA 039-402 (refer to the FOI Summary, dated June 29, 1994)
Experior™	NADA 141-508 (refer to the FOI Summary, dated November 6, 2018)
Rumensin™	NADA 095-735 (as published in the FEDERAL REGISTER (40 FR 58289) on December 16, 1975) (refer to the FOI Summaries, dated August 9, 1989, December 16, 1998, October 28, 2004, and December 1, 2006)

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   CVM did not require residue chemistry studies for this approval. NADA 039-402 (FOI Summary, dated June 29, 1994) contains a summary of studies supporting the approval of melengestrol acetate in cattle. NADA 141-508 (FOI Summary, dated November 6, 2018) contains a summary 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) contain summaries of studies supporting the approval of monensin in cattle. NADA 141-512 and NADA 141-514 (FOI Summaries, dated May 21, 2019) contain summaries of studies supporting the approval of melengestrol acetate, lubabegron, and monensin fed in combination in cattle.

2. Target Tissues and Marker Residues

   No reassessments for target tissues and marker residues were needed for this approval.

   The target tissue for melengestrol acetate is fat, and the marker residue is melengestrol acetate (21 CFR 556.380).

   The marker residue for lubabegron is parent lubabegron, and the target tissue is liver (21 CFR 556.370).

   Neither a target tissue nor a marker residue is codified for residues of monensin in cattle.

3. Tolerances

   A tolerance of 25 parts per billion (ppb) is established for melengestrol acetate in cattle fat (21 CFR 556.380).

   Tolerances for lubabegron in cattle are as follows: 10 ppb in liver, 3 ppb in muscle, 20 ppb in kidney (21 CFR 556.370).

   Tolerances for monensin in cattle are as follows: 0.10 parts per million (ppm) in liver, 0.05 ppm in muscle, kidney, and fat (21 CFR 556.420).

4. Withdrawal Period

   Results from study 1700188, summarized in the FOI Summaries for NADA 141-512 and NADA 141-514 (FOI Summaries, dated May 21, 2019) showed that residues of melengestrol acetate, lubabegron, monensin, and tylosin in cattle tissues were below their respective tolerances at 0-day withdrawal. The data support assignment of a 0-day withdrawal period for melengestrol acetate for cattle dosed at 0.25 to 0.50 mg/head/day in combination with lubabegron at 1.25 to 4.54 g/ton and monensin at 5 to 40 g/ton.

D. Analytical Method for Residues

1. Determinative Method

   The gas chromatography–mass spectrometry (GC-MS) method for determining melengestrol acetate in cattle fat is described in NADA 039-402 (FOI Summary, dated June 29, 1994). The liquid chromatography–mass spectrometry (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).

2. Confirmatory Method

   Confirmatory methods were not required for melengestrol acetate and monensin. An LC-MS/MS confirmatory method for lubabegron is described in NADA 141-508 (FOI Summary, dated November 6, 2018).

3. Availability of Method

   The validated analytical methods for analysis of residues of melengestrol acetate, lubabegron and monensin 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 039-402, NADA 141-508, and NADA 095-735.

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

User Safety Warnings: Not for use in humans. 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.

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 MGA®, Experior™ and Rumensin™ demonstrate that, when they are used according to the label, they are safe and effective for the conditions of use in the General

Information Section above. Additionally, data demonstrate that residues in food products derived from growing beef heifers fed in confinement for slaughter during the last 14 to 91 days on feed administered MGA®, 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.