Date of Approval: January 12, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-768

Ravantage® 9 and Ravantage® 45

(ractopamine hydrochloride Type A medicated article)

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

Finishing Swine

For increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter.

Sponsored by:

Huvepharma EOOD

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-768

B. Sponsor

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

Drug Labeler Code: 016592

C. Proprietary Name

Ravantage® 9 and Ravantage® 45

D. Drug Product Established Name

ractopamine hydrochloride Type A medicated article

E. Pharmacological Category

Beta-adrenergic agonist

F. Dosage Form

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

G. Amount of Active Ingredient

9 g/lb and 45.4 g/lb

H. How Supplied

25 lb (11.34 kg) bag

I. Dispensing Status

Over the counter (OTC)

J. Dosage Regimen

Feed ractopamine hydrochloride Type C medicated feed continuously as the sole ration to finishing swine weighing not less than 150 lbs for the last 45 to 90 lbs (group average) of weight gain prior to slaughter at a dietary concentration of 4.5 to 9.0 g of ractopamine hydrochloride per ton of feed.

K. Route of Administration

Oral, in feed

L. Species/Class

Finishing swine

M. Indications

For increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine, weighing not less than 150 lbs, fed a complete ration containing at least 16% crude protein for the last 45 to 90 lbs of gain prior to slaughter.

N. Reference Listed New Animal Drug (RLNAD)

Paylean™ 9 and Paylean™ 45; ractopamine hydrochloride Type A medicated article; NADA 140-863; 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. For certain dosage forms, the agency will grant a waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

Based on the formulation characteristics of the generic product, Huvepharma EOOD was granted a biowaiver for the generic product Ravantage® 9 and Ravantage® 45 (ractopamine hydrochloride Type A medicated article). The generic drug product is a Type A medicated article, 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 ingredient. The RLNAD is Paylean™ 9 and Paylean™ 45 (ractopamine hydrochloride Type A medicated article), sponsored by Elanco US Inc., under NADA 140-863, and was approved for use in finishing swine on December 22, 1999.

III. HUMAN FOOD SAFETY

The tolerances for residues and withdrawal period established for the RLNAD apply to the generic product. The following are assigned to this product for finishing swine:

A. Acceptable Daily Intake and Tolerances for Residues

The acceptable daily intake (ADI) for total residues of ractopamine hydrochloride is 1.25 µg/kg of body weight *per* day. The tolerances established for the RLNAD apply to the generic product. A tolerance of 0.15 parts *per* million (ppm) is established for ractopamine (the marker residue) in swine liver (the target tissue), and 0.05 ppm in swine muscle, under 21 CFR 556.570.

B. Withdrawal Period

A biowaiver was granted based on the solubility of the active pharmaceutical ingredient in Ravantage®. To determine if Ravantage® could be assigned the RLNAD's withdrawal period, the Agency evaluated an *in vitro* comparative solubility study that compared the solubility of the fully formulated Ravantage® and RLNAD products. The results of that study supported assigning Ravantage® the withdrawal period previously assigned to the RLNAD product. A withdrawal period of 0 days has been established for ractopamine Type A medicated article in finishing swine. The study that supported this withdrawal period for Ravantage® is described as follows.

Title: Demonstration of Solubility of Ractopamine Type A Medicated Articles in Aqueous Buffer Solutions. (Study No. SD-RDA10R)

Study Dates: March 17, 2018, to April 23, 2019

Study Location: Peshtera, Bulgaria

Study Objective: The objective of this study was to demonstrate similar *in vitro* solubility of the fully formulated Ravantage® (Huvepharma EOOD) and Paylean™ (Elanco US, Inc.; NADA 140-863) Type A medicated articles.

Test Article: Ravantage® (three lots of 45.4 g/lb. and two lots of 9 g/lb.)

Reference Article: Paylean™ (four lots of 45.4 g/lb. and five lots of 9 g/lb.)

Solubility Test Parameters: *In vitro* comparative solubility testing was conducted using a USP Type II apparatus (paddle). Table III.1 lists the parameters used during the solubility testing. The ractopamine concentration of the test samples was determined by a validated HPLC analytical method.

Table III.1. Solubility Testing Parameters

Parameter	Description
Buffers	USP pH 1.2, USP pH 4.6, and USP pH 7.5
Volume of Buffer	900 mL
Mass of Type A medicated article	0.54 ± 0.01 g (45.4 g/lb. articles) 2.70 ± 0.01 g (9 g/lb. articles)
Target Concentration	60 mg ractopamine/L
Temperature	38 ± 0.5°C
pH	1.2, 4.6, and 7.5
Paddle Speed	100 rpm
Sample Times	15 and 60 minutes

Statistical Methods: Solubility (Qi) was calculated according to the following equation.

$$Qi(\%) = \frac{\text{Ractopamine concentration of solubility sample (mg/mL)}}{\text{Theoretical concentration of ractopamine in dissolution vessel (mg/mL)}} \times 100$$

The 99th percentile tolerance interval with 95% confidence was calculated for the solubility values of the reference article. Individual solubility values for the test article were compared to these intervals.

Results: All test article Qi values were within the calculated 99th percentile tolerance intervals with 95% confidence for the reference article solubility. Across all three test conditions and all sampling timepoints, mean Qi values for the test article ranged from 96.43 ± 2.39% to 104.30 ± 1.84%.

Conclusions: The solubility data indicate that, under all three test conditions and at 15 and 60 minutes after starting the test, the solubility of Ravantage® is similar to the solubility of Paylean™. Therefore, based on these data, it is reasonable to expect that the absorption and metabolism of ractopamine and the disposition of resultant residues in edible swine tissues will be similar for Ravantage® and Paylean™. To this end, the data support assigning Ravantage® the withdrawal period previously assigned to the RLNAD for swine: 0-day withdrawal period.

C. Analytical Method for Residues

The validated analytical methods for analysis of residues of ractopamine 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

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Ravantage® 9 and Ravantage® 45:

NOT FOR HUMAN USE

WARNING: The active ingredient in Ravantage 9 and 45, ractopamine hydrochloride, is a beta-adrenergic agonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for use in humans. Keep out of the reach of children. The Ravantage 9 and 45 formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling Ravantage 9 and 45, 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 eyes thoroughly with water. If irritation persists, seek medical attention.

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 Ravantage® 9 and Ravantage® 45, 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 finishing swine treated with Ravantage® 9 and Ravantage® 45 will not represent a public health concern when the product is used according to the label.