Date of Approval: May 14, 2020

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-679

Optigrid® 45

(ractopamine hydrochloride Type A medicated article)

Type A medicated article for use in the manufacture of Type B and Type C medicated feeds

Cattle fed in confinement for slaughter

Complete Feed: For increased rate of weight gain, improved feed efficiency and increased carcass leanness in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

Top Dress Feed: For increased rate of weight gain and improved feed efficiency in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

Note: Carcass leanness effects are not an approved indication for use when feeding ractopamine by Top Dress Feeding methods.

Sponsored by:

Huvepharma EOOD

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I. GENERAL INFORMATION

A. File Number

ANADA 200-679

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 Westpark Drive
Peachtree City, GA 30269

C. Proprietary Name

Optigrid® 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 for use in the manufacture of Type B and Type C medicated feeds

G. Amount of Active Ingredient

45.4 g/lb (100 g/kg)

H. How Supplied

25 lb (11.34 kg) bags

I. Dispensing Status

Over-the-counter (OTC)

J. Dosage Regimen

Complete Feed:

Indications	Appropriate concentration of ractopamine in Type C medicated feed[a]	Ractopamine (mg/hd/d)
Increased rate of weight gain and improved feed efficiency	8.2 to 24.6 g/ton (9 ppm to 27 ppm)	70 – 430
Increased rate of weight gain, improved feed efficiency, and increased carcass leanness	9.8 to 24.6 g/ton (11 ppm to 27 ppm)	90 – 430

[a]Based on 90% Dry Matter Basis

Directions for use (complete feed): Feed continuously to cattle fed in confinement for slaughter as the sole ration for the last 28 to 42 days on feed.

Top Dress Feed:

Indications	Appropriate concentration of ractopamine in Type C medicated feed[a]	Ractopamine (mg/hd/d)
Increased rate of weight gain and improved feed efficiency	Appropriate concentration of ractopamine in a minimum of 1.0 lb Top Dressed Type C medicated feed[a] (maximum of 800 g/ton)	70 – 400

[a]Based on 90% Dry Matter Basis

Directions for use (Type C medicated top dress feed): Feed continuously to cattle fed in confinement for slaughter a Type C Medicated Feed containing up to a maximum of 800 g/ton ractopamine (see mixing direction table) to provide 70 to 400 g/head/day for the last 28 to 42 days on feed. Type C Medicated Top Dress Feed must be fed in a minimum of 1.0 lb per head per day to provide 70 to 400 mg/head/day.

K. Route of Administration

Oral

L. Species/Class

Cattle fed in confinement for slaughter

M. Indications

Complete Feed: For increased rate of weight gain, improved feed efficiency and increased carcass leanness in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.
Top Dress Feed: For increased rate of weight gain and improved feed efficiency in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.
Note: Carcass leanness effects are not an approved indication for use when feeding ractopamine by Top Dress Feeding methods.

N. Reference Listed New Animal Drug (RLNAD)

Optaflexx™ 45; ractopamine hydrochloride Type A medicated article; NADA 141-221; 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 Optigrid® 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 Optaflexx™ 45 (ractopamine hydrochloride Type A medicated article), sponsored by Elanco US Inc., under NADA 141-221 and, was approved for use in cattle fed in confinement for slaughter on June 13, 2003.

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 cattle:

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 0.09 parts per million (ppm) is established for ractopamine (the marker residue) in cattle liver (the target tissue), and 0.03 ppm in cattle muscle, under 21 CFR §556.570.

B. Withdrawal Period

A biowaiver was granted based on the solubility of the active pharmaceutical ingredient in Optigrid® 45. To determine if Optigrid® 45 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 Optigrid® 45 and RLNAD products. The results of that study supported assigning Optigrid® 45 the withdrawal period previously assigned to the RLNAD product. A withdrawal period of 0 days has been established for ractopamine hydrochloride Type A

medicated article in cattle fed in confinement for slaughter. The study that supported this withdrawal period for Optigrid® 45 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 Optigrid® 45 (Huvepharma EOOD) and Optaflexx™ 45 (Elanco US, Inc.; NADA 141-221) Type A medicated articles.

Test Article: Three lots of Optigrid® 45 (45.5 g/lb.)

Reference Article: Four lots of Optaflexx™ 45 (45.5 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
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 solubility values were within the calculated 99th percentile tolerance intervals with 95% confidence for the reference article solubility. Table III.2 presents the solubility results for the test and reference articles and the 99th percentile tolerance interval with 95% confidence for the reference article solubility.

Table III.2. Mean (± standard deviation) solubility (Qi) values for test and reference articles and the 99th percentile tolerance interval with 95% confidence for the reference article solubility.

Test Condition	Time	Mean Reference Article Qi (%)	Mean Test Article Qi (%)	Reference Article Qi Tolerance Interval (99^{th}/95%)
pH 1.2 Buffer	15	100.52 ± 1.07	99.93 ± 0.76	93.49 – 107.56
pH 1.2 Buffer	60	104.20 ± 1.30	101.87 ± 0.51	95.65 – 112.75
pH 4.6 Buffer	15	97.76 ± 0.75	97.53 ± 1.00	92.81 – 102.71
pH 4.6 Buffer	60	101.88 ± 0.70	100.13 ± 0.32	97.28 – 106.48
pH 7.5 Buffer	15	96.10 ± 0.91	96.43 ± 2.39	90.07 – 102.13
pH 7.5 Buffer	60	102.04 ± 0.86	99.60 ± 0.92	96.33 – 107.75

Conclusions: The solubility data indicate that, under all three test conditions and at 15 and 60 minutes after starting the test, the solubility of Optigrid® 45 is similar to the solubility of Optaflexx™ 45. 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 cattle tissues will be similar for Optigrid® 45 and Optaflexx™ 45. To this end, the data support assigning Optigrid® 45 the withdrawal period previously assigned to the RLNAD for cattle: 0-day withdrawal period.

C. Analytical Method for Residues

The validated analytical method for analysis of residues of ractopamine 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 Summary 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 Optigrid® 45:

NOT FOR HUMAN USE

WARNING: The active ingredient in Optigrid® 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 Optigrid® 45 formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling Optigrid® 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

This information submitted in support of this ANADA satisfies the requirements of section 512(c)(2) of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that Optigrid® 45, when used according to the label, is safe and effective.

Additionally, data demonstrate that residues in food products derived from cattle treated with Optigrid® 45, will not represent a public health concern when the product is used according to the label.