Date of Approval: May 6, 2019

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-288

EXCENEL® RTU EZ

ceftiofur hydrochloride

Injectable Suspension

Swine

This supplement provides for an increase in the maximum injection site volume in swine from 5 mL to 15 mL. The larger maximum injection site volume will reduce the number of injections needed in larger pigs.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-288

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

EXCENEL® RTU EZ

D. Drug Product Established Name

Ceftiofur hydrochloride

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Injectable suspension

G. Amount of Active Ingredient

50 mg ceftiofur equivalents (CE)/mL

H. How Supplied

100 mL and 250 mL vials

I. Dispensing Status

Rx

J. Dosage Regimen

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents (CE)/lb (3 to 5 mg CE/kg) body weight (BW) (1 mL of sterile suspension per 22 to 37 lb BW). Treatment should be repeated at 24 hour intervals for a total of three consecutive days. Do not inject more than 15 mL per injection site.

K. Route of Administration

Intramuscular injection

L. Species/Class

Swine

M. Indication

Swine: EXCENEL® RTU EZ is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Salmonella* Choleraesuis and *Streptococcus suis.*

N. Effect of Supplement

This supplement provides for an increase in the maximum injection site volume in swine from 5 mL to 15 mL. The larger maximum injection site volume will reduce the number of injections needed in larger pigs.

II. EFFECTIVENESS

Summary: FDA concluded that there will be no negative impact on the effectiveness of EXCENEL® RTU EZ associated with injection of volumes up to 15 mL within a single injection site in swine. As summarized below, effectiveness of EXCENEL® RTU EZ in swine for the labeled indication and dosage regimen at volumes up to 5 mL per injection site has previously been demonstrated. Pharmacokinetic data were used to determine that the increase in injection site volume (i.e., increasing from 5 mL to 15 mL per injection site) did not compromise drug absorption, thereby altering plasma concentrations enough to decrease effectiveness.

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage regimen. EXCENEL® RTU EZ is a reformulation of another currently approved ceftiofur hydrochloride injectable product, EXCENEL® RTU Sterile Suspension (NADA 140-890). The Freedom of Information (FOI) Summary for the original approval of EXCENEL® RTU Sterile Suspension (NADA 140-890) dated April 26, 1996, contains dosage characterization information for swine.

B. Substantial Evidence

The FOI Summary for the original approval of EXCENEL® RTU Sterile Suspension (NADA 140-890) dated April 26, 1996, contains substantial evidence of the effectiveness of ceftiofur hydrochloride in swine for injection volumes up to 5 mL within a single injection site. The FOI Summary for the original approval of EXCENEL® RTU EZ (NADA 140-288) dated July 1, 2008, confirmed that with respect to effectiveness, EXCENEL® RTU Sterile Suspension and EXCENEL® RTU EZ are considered bioequivalent.

This supplemental approval provides for an increase in the maximum injection site volume for pigs from 5 mL to 15 mL of EXCENEL® RTU EZ. A pharmacokinetic comparison was conducted to determine if the larger volumes of drug could compromise drug absorption, resulting in plasma concentrations that were not of sufficient duration for a time dependent antimicrobial such as ceftiofur.

Based on historical pharmacokinetic and clinical data, the length of time over which the concentration of ceftiofur and desfuroylceftiofur-related metabolites in plasma (hours) remained above 0.2 µg/mL (t > 0.2 µg/mL) can be used as a pharmacodynamic surrogate in the assessment of product effectiveness. Therefore, the basis for effectiveness was the ability of EXCENEL® RTU EZ injected at volumes up to 15 mL per site to maintain total desfuroylceftiofur concentrations at levels equal to or greater than those associated with injection volumes of up to 5 mL per site.

The pharmacokinetic data from the bioequivalence study conducted to support the 2008 approval of EXCENEL® RTU EZ were used for the comparison of t > 0.2 µg/mL between injection site volumes of EXCENEL® RTU Sterile Suspension at ≤ 5 mL and > 5 mL to 12 mL. The study was a three-period, two-treatment crossover study in 16 pigs with a 28-day washout between periods. The study was conducted over a two month period in rapidly growing pigs. Therefore, to maintain a constant mg/kg dose, the injection site volumes for Periods 1, 2, and 3 increased, ranging from 4.9 to 5.7 mL, 7.2 to 8.5 mL, and 8.6 to 12.0 mL respectively. Statistical analysis allowed for an extrapolation of these findings to 15 mL per site.

The results demonstrated that t > 0.2 µg/mL increased during periods 1, 2, and 3. However, due to the change in age and body weight of the pigs during the three periods in this study, the effects of volume, age (maturation), and body weight on drug pharmacokinetics (metabolism, distribution, and absorption) were confounded. The results also suggested a decrease in relative clearance corresponding to age as the animals matured. Therefore, it was not possible to conclude that the increase in t > 0.2 µg/mL was attributable only to injection volume. Because only older and heavier pigs will be receiving the larger volumes, it was concluded that, irrespective of the reason for the increase in t > 0.2 µg/mL, there is sufficient information that there will be no negative impact on effectiveness associated with injection of volumes up to 15 mL within a single injection site. The inability to differentiate the impact of relative clearance (as a function of age) versus injection site volume on t > 0.2 µg/mL does not adversely affect this conclusion. However, it is important to note that this relative bioavailability assessment is appropriate only for the approved conditions of use. Under any other circumstances, applying this type of relative bioavailability analysis to a population with such a marked change in relative clearance would not be appropriate.

III. TARGET ANIMAL SAFETY

Summary: FDA concluded that there will be no negative impact on the target animal safety of EXCENEL® RTU EZ associated with injection of volumes up to 15 mL within a single injection site in swine. As summarized below, the systemic margin of safety of EXCENEL® RTU EZ in swine for the labeled indication and dosage regimen at volumes up to 5 mL per injection site has previously been demonstrated. The systemic safety of an increase in maximum injection site volume for EXCENEL® RTU EZ to 15 mL was demonstrated using pharmacokinetic data to show that there was minimal increase in plasma drug concentrations at higher injection site volumes (up to 12 mL) compared to the previously evaluated volume (5 mL). Based on this information, it was concluded that volumes of 15 mL per injection site will also

remain within the previously established systemic margin of safety. Additionally, an injection site tolerance study evaluated injection sites in pigs administered EXCENEL® RTU EZ by intramuscular (IM) injection at 15 mL per injection site for three consecutive days. There were no abnormal changes in general health and no visible or palpable injection site abnormalities during the study. Gross necropsy and histopathology observations of the injection sites consistent with acute or chronic inflammation were observed up to 42 days post-injection; such findings are common with injectable products and were considered to be at an acceptable level.

A. Systemic Safety

The systemic safety of EXCENEL® RTU EZ is supported by the margin of safety study for the 1992 supplemental approval of Naxcel® Sterile Powder (NADA 140-338), a relative bioavailability study to support the approval of EXCENEL® RTU Sterile Suspension in swine (NADA 140-890), and a study to confirm the bioequivalence of EXCENEL® RTU Sterile Suspension to EXCENEL® RTU EZ (NADA 141-288, September 2013).

Because EXCENEL® RTU EZ and EXCENEL® RTU Sterile Suspension are bioequivalent, the safety of injection volumes up to 15 mL was supported by a comparison of drug exposure of EXCENEL® RTU Sterile Suspension when injected at volumes of 5 and 12 mL. When compared to the younger pigs administered injection volumes of approximately 5 mL, there was only a minor increase in the maximum plasma concentration (C_{max}) in the older pigs administered injection volumes up to 12 mL. Based on this minor change in drug exposure between 5 mL and 12 mL per injection site, it is concluded that volumes of 15 mL per injection site will also remain within the previously established systemic margin of safety. Therefore, it was determined that the higher injection volumes administered to older and larger pigs (up to 15 mL per injection site) would not pose any systemic safety concerns.

B. Injection Site Tolerance Study

Title: "Injection Site Tolerance of a Revised Formulation of EXCENEL RTU EZ Sterile Suspension in Adult Swine." (Study Number A325N-US-15-226)

Study Dates: November 2015 to April 2016

Study Location: Tulare, CA

Study Design:

Objective: To evaluate the injection site tolerance of EXCENEL® RTU EZ after IM administration in the neck of adult swine at the maximum proposed injection site volume of 15 mL per injection site for three consecutive days. The study was conducted in compliance with the Good Laboratory Practice (GLP) Regulations (21 CFR Part 58) and Organisation for Economic Co-operation and Development (OECD) Principles of GLP, as well as Guidance for Industry (GFI) #185 (Target Animal Safety for Veterinary Pharmaceutical Products - VICH GL43) and test facility SOPs.

Study Animals: Sixteen healthy, adult commercial crossbred pigs (9 females and 7 males), weighing 184.5 to 247.5 kg, were enrolled in the study. Pigs were housed individually in indoor pens.

Experimental Design: Pigs were randomly assigned to pen, treatment group, and necropsy day. Eight pigs each were assigned to receive either EXCENEL® RTU EZ or saline. Within each treatment group, two pigs were assigned to each necropsy day (Day 7, 14, 28, or 42). The study veterinarian, study pathologist, and personnel making general health observations were masked to treatment group identification.

Drug Administration: The test article was EXCENEL® RTU EZ (50 mg ceftiofur equivalents/mL) sterile suspension, as the currently marketed formulation. The negative control article was a sterile saline (0.9% NaCl) injectable solution. The assigned treatments were administered at a dose volume of 15 mL by intramuscular injection in the neck once daily on Days 0, 1, and 2.

Measurements and Observations: General health observations were conducted on all animals at least once daily from acclimation (Day -14) until the last day of the in-life phase (Day 42). Clinical observations were conducted by the study veterinarian at least once daily on Days -14, -1, 0, 1, 2, 7, 14, 28, and 42. Injection site evaluations (visual observation and palpation) were conducted on Day -14, Day -1, and from Day 0 until Day 42. Pigs were euthanized on Days 7, 14, 28 or 42 (two saline-treated pigs and two EXCENEL® RTU EZ-treated pigs at each time point).

Results:

General Health and Clinical Observations: There were no abnormal clinical observations or general health observations related to test article administration. All enrolled animals completed the study.

Injection Site Evaluations: No erythema, heat, sensitivity, firmness, necrosis, drainage, or swelling was observed at any injection site on any study day.

Gross Necropsy and Histopathology: Gross necropsy observations revealed observations consistent with inflammation (discoloration, edema, and/or nodules) of one or more injection sites in all saline-treated and EXCENEL® RTU EZ-treated pigs necropsied on Day 7 and Day 14, in one saline-treated and both EXCENEL® RTU EZ-treated pigs necropsied on Day 28, and in all saline-treated and EXCENEL® RTU EZ-treated pigs necropsied on Day 42. Histopathological evaluation was consistent with the gross necropsy findings (active or chronic inflammation) in all EXCENEL® RTU EZ-treated pigs. Microscopic findings were uncommon at saline-injected sites collected on Days 7, 14, 28, and 42.

Conclusion: The study demonstrated that EXCENEL® RTU EZ was well tolerated when injected IM in adult pigs at a maximum dose volume of 15 mL per injection site for three consecutive days. Grossly observable lesions were present in the injection sites beyond the slaughter withdrawal period, which may result in trim loss of edible tissues at slaughter.

IV. HUMAN FOOD SAFETY

Summary: The toxicological safety and the microbial food safety of EXCENEL® RTU EZ were established during the original approval under NADA 141-288. The codified tolerances for ceftiofur in edible swine tissues were established during the original approval of NADA 140-890. Therefore, for the supplemental approval to increase the maximum injection site volume from 5 mL to 15 mL in pigs treated with EXCENEL® RTU EZ, the Agency reviewed a residue depletion study during the Human Food Safety evaluation. This study demonstrated that ceftiofur residues are less than the codified tolerance in swine kidney at 6 days after the last treatment with EXCENEL® RTU EZ administered as a 15-mL intramuscular injection at a dose of 1.36 to 2.27 mg ceftiofur equivalents/lb body weight (3.0 to 5.0 mg/kg). It was not necessary to measure injection site residues in the study because a previous study demonstrated that injection site residues are significantly less than the value used by the Agency to make decisions regarding the safety of ceftiofur residues at the injection site. An analytical method for monitoring ceftiofur residues in edible swine tissues was developed during the original approval of EXCENEL® RTU EZ under NADA 141-288.

A. Antimicrobial Resistance

The agency determined that an increase in the maximum allowable injection site volume of EXCENEL® RTU EZ (ceftiofur hydrochloride) from 5 mL to 15 mL should not significantly impact public health with respect to selection or emergence of antimicrobial-resistant bacteria in or on treated swine. This supplemental approval involves no change in formulation, dosage, route of administration, or duration of use; therefore, further evaluation of microbial food safety (antimicrobial resistance) associated with increasing the maximum allowable injection site volume of EXCENEL® RTU EZ (ceftiofur hydrochloride) was not necessary.

B. Effects of Residues on Human Intestinal Flora

CVM did not require additional information for the impact of residues on human intestinal flora for this supplemental approval. The FOI Summary for NADA 141-288, dated September 13, 2013, contains a summary of all information used to assess the impact of residues on human intestinal flora.

C. Toxicology

Reassessment of the toxicological Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD) was not needed for this supplemental approval. The FOI Summaries for the original approval of NADA 140-338, dated January 25, 1988; NADA 140-890, dated April 26, 1996; NADA 141-209, dated September 5, 2003; and NADA 141-235, dated June 18, 2004, contain summaries of all toxicology studies and information.

D. Establishment of the Final ADI and ARfD

The final ADI is the toxicological ADI of 30 µg/kg bw/day for total residues of ceftiofur derived from 90-day oral studies in dogs and rats. The ARfD is 0.830 mg/kg bw for total residues of ceftiofur derived from studies conducted in

the guinea pig model of ceftiofur hypersensitivity and cross hypersensitivity between penicillin G and ceftiofur. The codified ADI and ARfD are listed under 21 CFR §556.113.

E. Safe Concentrations for Total Residues in Edible Tissues and Injection Sites

Reassessment of the safe concentrations for total residues of ceftiofur was not needed for this approval. The safe concentrations for total residues of ceftiofur in the individual edible tissues of swine are 4.4 parts per million (ppm) for muscle, 13.2 ppm for liver, 26.4 ppm for kidney, 26.4 ppm for fat, 0.32 ppm for milk, and 166 ppm for the injection site. These values reflect the partition of the ADI between meat (73% of the ADI) and milk (27% of the ADI).

F. 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 supplemental approval. The FOI Summary for the original approval of NADA 140-890, dated April 26, 1996, contains a summary of the total residue and metabolism studies for ceftiofur in swine.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this supplemental approval. The FOI Summary for the original approval of NADA 140-890, dated April 26, 1996, contains summaries of comparative metabolism studies for ceftiofur in swine.

c. Study to Establish Withdrawal Period

Title: Determination of Ceftiofur and Desfuroylceftiofur-Related Residues in Kidney Tissue of Swine Receiving EXCENEL RTU EZ (50 mg/mL) for 3 Consecutive Days by Intramuscular Injection at a Dose Rate of 5 mg/kg with at least 15 mL per Dose (Study No. A423N-US-18-287)

Study Dates: May 23, 2018 to August 27, 2018

Study Locations: In-life Animal Phase: Richland, MI, USA

Analytical Phase: Kalamazoo, MI, USA

Study Design:

Objective: The objective of the study was to determine the concentrations of ceftiofur and desfuroylceftiofur-related residues, as measured by the marker residue desfuroylceftiofur acetamide (DCA), in kidney tissues from pigs treated with three daily intramuscular injections of EXCENEL® RTU EZ at a dose of 5.0 mg ceftiofur/kg of body weight administered in an injection

site volume of 15 mL. This study was conducted in accordance with the Good Laboratory Practices Regulations (GLPs; 21 CFR §58).

Study Animals: Thirty-six pigs (18 gilts and 18 barrows), weighing 147.0 kg to 181.2 kg were used in this study.

Experimental Design: Pigs were assigned randomly to one of six groups (Table IV.1) such that each group contained three males and three females (n = 6 per group).

Drug Administration: Pigs were treated once daily for three consecutive days with an intramuscular injection of 5.0 mg ceftiofur/kg of body weight in the following sequence of injection sites: upper left neck, upper right neck and, finally, lower left neck. All pigs were treated with at least a single 15-mL injection of EXCENEL® RTU EZ on each dosing day. If a dose volume greater than 15 mL was required, the dose was split between two syringes with the first 15 mL injected in the primary injection site and the remaining volume administered within 1.5 inches of the primary injection site.

Measurements and Observations: At the assigned withdrawal times (Table IV.1), pigs were slaughtered, and kidney samples were collected. The kidney samples were assayed for concentrations of ceftiofur and desfuroylceftiofur-related residues, measured as DCA, by a validated HPLC-UV procedure. The method's limit of quantification (LOQ) was 0.1 ppm. Kidney concentrations of DCA less than the method LOQ were excluded from the analyses.

Statistical Method: The data were analyzed using a statistical algorithm that calculated the upper tolerance limit for kidney DCA concentrations for the 99th percentile with 95% confidence.

Results: Mean (± standard deviation) concentrations of DCA in kidney samples are presented in Table IV.1.

Table IV.1. Mean (± standard deviation) concentrations of ceftiofur residues (measured as desfuroylceftiofur acetamide (DCA)) in kidney tissues from pigs treated once daily for three consecutive days with an intramuscular injection of 5.0 mg ceftiofur/kg of body weight administered in an injection site volume of 15 mL

Treatment Group	Slaughter Time (Hours After Last Treatment)	Kidney DCA Concentration (ppm)
1	12	5.37 ± 1.74
2	24	2.58 ± 0.70
3	48	0.78 ± 0.20
4	72	0.43 ± 0.16
5	120	0.13 ± 0.02
6	168	BLOQ[1]

[1] BLOQ, Below the limit of quantification (0.1 ppm)

The upper tolerance limit for kidney DCA concentrations for the 99th percentile with 95% confidence was less than the codified kidney tolerance in swine (0.25 ppm) at 6 days after the last injection.

Conclusions: The data from Study A423N-US-18-287 support assigning a 6-day withdrawal period to EXCENEL® RTU EZ for pigs treated for three consecutive days with an intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb body weight (3.0 to 5.0 mg/kg) administered in an injection site volume of up to 15 mL.

For research purposes a value of 80 ppm DCA has been established for making decisions regarding the safety of the injection site (see the FOI Summary for NADA 141-235 [EXCEDE for Swine, ceftiofur crystalline free acid] dated June 18, 2004). Residue depletion data summarized in the FOI Summary for NADA 141-288, dated July 1, 2008, demonstrate that injection site residues are significantly below 80 ppm. As such, it was not necessary to measure residues at the injection site in Study A423N-US-18-287.

2. Target Tissue and Marker Residue

A reassessment of the target tissue and marker residue was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 140-890, dated April 26, 1996, contains summaries of the information used to determine the target tissue and marker residue for ceftiofur in swine.

The target tissue is kidney, and the marker residue is desfuroylceftiofur (21 CFR §556.113).

3. Tolerances

A reassessment of the tolerances was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 140-890, dated April 26, 1996, contains summaries of the information used to establish the tolerances for ceftiofur in swine.

The tolerances for desfuroylceftiofur (marker residue) are 0.25 ppm in swine kidney (target tissue), 3 ppm in swine liver, and 2 ppm in swine muscle (21 CFR §556.113).

4. Withdrawal Periods

The injection site volume affects the withdrawal period in swine.

EXCENEL® RTU EZ is assigned a 6-day withdrawal period in swine treated for three consecutive days with an intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb body weight (3.0 to 5.0 mg/kg) administered in an injection site volume greater than 5 mL up to the maximum injection site volume of 15 mL.

EXCENEL® RTU EZ is assigned a 4-day withdrawal period in swine treated for three consecutive days with an intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb body weight (3.0 to 5.0 mg/kg) administered in an injection site volume less than or equal to 5 mL (FOI Summary for NADA 141-288, dated September 13, 2013).

G. Analytical Method for Residues

The FOI Summary for the original approval of NADA 141-288, dated July 1, 2008, contains the analytical method summary for ceftiofur in swine.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to EXCENEL® RTU EZ:

Not for human use. Keep out of reach of children.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The safety data sheet contains more detailed occupational safety information. To obtain a safety data sheet (SDS) or to report any adverse event please call 1-888-963-8471.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that EXCENEL® RTU EZ, when used according to the label, is safe and effective for the treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae*, P*asteurella multocida*, *Salmonella* Choleraesuis and *Streptococcus suis*. Additionally, data demonstrate that residues in food products derived from species treated with EXCENEL® RTU EZ will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues, 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 in animals in order to slow or prevent any potential for the development of bacterial resistance to antimicrobial drugs.

B. Exclusivity

This supplemental approval for EXCENEL® RTU EZ qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included a safety study. This exclusivity begins as of the date of our approval letter and only applies to the increase in the maximum injection site volume in swine from 5 mL to 15 mL.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information

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