PIG HEALTH TODAY®

ISSUE 15

NEWS ABOUT PIG HEALTH PRODUCTS

An interview with
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Director, US Regulatory Affairs
Zoetis

Do's and don'ts of cephalosporin use in swine

Q: Cephalosporins have been key to successful management of respiratory disease in swine. However, they are medically important antimicrobials in human medicine, and FDA has understandably set limits on their use. Are there any issues you're aware of regarding compliance with cephalosporin use throughout the pork industry?

JH: Swine producers and veterinarians have done a great job adhering to the rules regarding cephalosporin use in food animals. We do get questions from time to time, however, when certain situations lead to uncertainty about compliance, especially regarding extralabel (off-label) use.[1]

Q: Are there any situations when extralabel use of a cephalosporin is permitted?

JH: If you have a group of pigs with an illness due to a pathogen that's not on the label and for which there's no approved therapy — salmonellosis due to *Salmonella*, for example — using a cephalosporin would be justified. Another instance would be if an approved therapy has failed and it's the veterinarian's professional opinion that a cephalosporin may be effective.

> "If you have a group of pigs with an illness due to a pathogen that's not on the label and for which there's no approved therapy — salmonellosis due to *Salmonella*, for example — using a cephalosporin would be justified."

Q: Let's say a group of young pigs is unthrifty but doesn't have respiratory signs. If it can be documented in sacrificed pigs that *Streptococcus suis* is present, can they be treated with a cephalosporin?

JH: Yes, they can, as long as the veterinarian believes their poor health is likely due to *S. suis*.

Q: What about extralabel use of a cephalosporin for the prevention of a disease?

JH: Never. FDA defines prevention as treatment of a group of animals when none have clinical signs of disease or in a situation where a disease is likely to occur if the medication isn't administered. Don't do it.

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> "If [veterinarians] see pigs coughing and breathing hard, they can recommend a cephalosporin if they believe the problem is due to one of the pathogens on the label. Laboratory testing is not required."

Q: The labels for Naxcel® (ceftiofur sodium) and Excenel® RTU EZ (ceftiofur hydrochloride) say swine "should be treated for a total of 3 consecutive days." What if unforeseen circumstances on the farm get in the way of following that exact protocol?

JH: Veterinarians and producers should make every effort to be good antibiotic stewards and follow the recommendations on the product's label. Those directions for use were deemed by FDA to be most safe and effective after reviewing large pivotal studies with the product.

Using those antibiotics at any dose or frequency greater than what's recommended would be considered extralabel and, as such, would not be allowed under the current regulation. Overmedicating also would lead to higher costs and potentially violative residues. For those reasons, exceeding the dose or treatment frequency indicated on the label rarely occurs.

Q: Let's look at the other scenario. On the farm, an unexpected labor shortage or extremes in the weather could potentially stand in the way of treating all pigs for 3 consecutive days. What are the veterinarian's options in those situations?

JH: Again, every effort should be made to follow the dose and dosing duration provided on the label. However, when those unforeseen, real-world circumstances do arise, it comes down to the attending veterinarian's judgement to modify treatment from the product label.

For example, how did the pigs respond to the initial treatments? Are they doing better from a health and welfare standpoint? In the end, FDA defers to the veterinarian's expertise, records and clinical observations to ensure that every effort was made to provide good care and use the products in a safe, judicious and efficacious manner.

Q: Are there other treatment options to ensure administration compliance?

JH: Yes. Veterinarians and producers also could consider using sustained-release antimicrobials such as Draxxin® 25 (tulathromycin) or Excede® (ceftiofur crystalline free acid), which require only one dose. The tradeoff with those products is the longer withdrawal period — 5 days for Draxxin and 14 days for Excede, versus 4 days for Naxcel and 4 days for Excenel RTU EZ (when injection site volumes are 5 mL).

Q: One of the indications for Naxcel, Excede (ceftiofur crystalline free acid) and Excenel RTU EZ is for *control* of respiratory disease associated with certain pathogens. FDA's definition of control is a "drug administered to a group of animals when a proportion of the animals in the group exhibit clinical signs of disease." Is there a minimum number of animals that have to have clinical signs before the group can be treated with a cephalosporin?

JH: If you use FDA criteria for experimental field trails as a guide — specifically, Guidance for Industry 178[2]— at least 15% of the group should be exhibiting signs of disease before treatment. This is a starting point, however. In our discussions with regulators about study protocols, FDA's Center for Veterinary Medicine was open to discussion about reducing that threshold to 10% incidence level to reduce mortality.[3] In the field, if a group of animals has a history of a disease that has been documented in medical records and a few start breaking with signs of the same disease, treatment may be justified. Once again, it comes down to the attending veterinarian's judgement.

Q: How important is laboratory evidence of infection for justifying extralabel use of a cephalosporin?

JH: Veterinarians are allowed to practice veterinary medicine. If they see pigs coughing and breathing hard, they can recommend a cephalosporin if they believe the problem is due to one of the pathogens on the label. Laboratory testing is not required.

However, if the disease gets more severe and pigs are dying, it would be prudent to conduct post-mortems and send samples for testing. Again, this isn't required, but it's good practice.

Q: If young pigs on a farm don't have signs of respiratory disease but they have joint issues and associated lameness — a condition that can be caused by *S. suis* — can they be treated with a cephalosporin if it's known their sows are positive for this pathogen? Or would that be considered extralabel, preventive use?

JH: This is a good example of an infectious disease that is not on the label but where extralabel use would be permitted. The cephalosporin must still be prescribed by the veterinarian according to the label at the approved dose, route of administration, frequency and duration of administration.

Q: Is it OK to reconstitute Naxcel to a desired potency for lesser injection volume?

JH: Reconstitution with different volumes of sterile water is acceptable as long as the total milligrams an animal receives is according to the label — 3 to 5 mg/kg.

Q: What documentation is acceptable to FDA regarding the use of a cephalosporin?

JH: When a group of pigs is treated with a cephalosporin, don't rely on anyone's memory. Write it down, date it and sign it. A document that's handwritten, dated and signed is golden. The records should include the estimated number of pigs in the facility, the disease and the dosage received, which of course must comply with the label. There should also be an

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"When a group of pigs is treated with a cephalosporin... Write it down, date it and sign it. A document that's handwritten, dated and signed is golden."

estimate of the total number of pigs treated. I say "estimate" because it's often not possible to get a completely accurate head count with a large group of pigs. The FDA puts a high value on handwritten, hard copies of medical records.

Q: If there's a residue violation with a cephalosporin, will handwritten records adequately document compliance for the prescribing veterinarian?

JH: Yes, assuming the cephalosporin was prescribed appropriately. Veterinarians also have the responsibility of ensuring that producers observe required withdrawal periods. I'm aware of several residue-violation cases where veterinarians who prescribed a cephalosporin had accurate treatment records demonstrating compliance with the label and that accounted for the necessary withdrawal time. FDA found the veterinarians did nothing wrong.

Q: What records should be kept when the veterinarian can't get to the farm and provides a prescription over the phone?

JH: First, there should be a veterinarian-client-patient relationship, as defined by FDA. The swine facility should keep a record of exactly what was prescribed for which animals and when. But veterinarians should make note in their own dated records about who contacted them and what was prescribed. FDA understands that veterinarians can't always get to a farm, but it may check to see if records from the facility and the veterinarian match.

Q: Are there any common mistakes you see regarding the use of cephalosporins in swine?

JH: It doesn't happen often, and I know of this happening with different types of drugs, not just cephalosporins, but there are cases where farm workers weren't clear on the instructions or simply grabbed the wrong bottle. To me, this underscores the need for producers to carefully select the employees they permit to administer any medications, not just cephalosporins, and to provide careful training.

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[1] Cephalosporin Order of Prohibition Questions and Answers [Internet] FDA [cited August 25, 2019] Available from: https://www.fda.gov/animal-veterinary/antimicrobial-resistance/cephalosporin-order-prohibition-questions-and-answers.

[2] Guidance for Industry 178, Recommended Study Design and Evaluation of Effectiveness Studies for Swine Respiratory Disease Claims. U.S. Department of Health and Human Services Food and Drug Administration Center for Veterinary Medicine October 1, 2007.

[3] Personal communication.

For more information, contact John Hallberg (john.hallberg@zoetis.com) or your Zoetis representative.

IMPORTANT SAFETY INFORMATION

People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to NAXCEL. NAXCEL has a pre-slaughter withdrawal time of four days. Do not use in animals found to be hypersensitive to the product. See full Prescribing Information (attached).

People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to EXCENEL RTU EZ. Do not use in swine found to be hypersensitive. Withdraw 6 days prior to slaughter when injection site volumes are greater than 5 mL up to 15 mL per injection site and 4 days prior to slaughter when injection site volumes are less than or equal to 5 mL per injection site. See full Prescribing Information (attached).

Withdraw DRAXXIN/DRAXXIN 25 five (5) days prior to slaughter. Do not use in animals known to be hypersensitive to the product. See full Prescribing Information (attached).

People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to EXCEDE. Do not use in swine found to be hypersensitive to the product. Pre-slaughter withdrawal time is 14 days following the last dose. See full Prescribing Information (attached).

Notes

Naxcel®

brand of ceftiofur sodium sterile powder

For intramuscular and subcutaneous injection in cattle only. For intramuscular injection in swine, sheep, goats, and horses. For subcutaneous injection only in dogs, day-old chickens and day-old turkey poults. This product may be used in lactating dairy cattle, sheep, and goats.

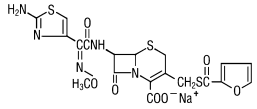
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle, swine, chickens and turkeys for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

NAXCEL Sterile Powder contains the sodium salt of ceftiofur which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of the reconstituted drug contains ceftiofur sodium equivalent to 50 mg ceftiofur. The pH was adjusted with sodium hydroxide and monobasic potassium phosphate.

Chemical Structure of Ceftiofur Sodium



Chemical Name of Ceftiofur Sodium

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[(2-furanylcarbonyl)thio] methyl]-8-oxo-, monosodium salt, [6R-[6α,7β(Z)]]-

RECONSTITUTION OF THE STERILE POWDER

NAXCEL Sterile Powder should be reconstituted as follows:

1 gram vial–Reconstitute with 20 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

4 gram vial–Reconstitute with 80 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

Shake thoroughly prior to use.

INDICATIONS

Cattle

NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*. NAXCEL Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

Swine

NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis*.

Sheep

NAXCEL Sterile Powder is indicated for treatment of sheep respiratory disease (sheep pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Goats

NAXCEL Sterile Powder is indicated for treatment of caprine respiratory disease (goat pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Horses

NAXCEL Sterile Powder is indicated for treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus*.

Dogs

NAXCEL Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis*.

Day-Old Chicks

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old chicks.

Day-Old Turkey Poults

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old turkey poults.

DOSAGE AND ADMINISTRATION

Cattle

Administer to cattle by intramuscular or subcutaneous injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., for respiratory disease, extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite; and for foot rot, extent of swelling, lesion and severity of lameness).

Swine

Administer to swine by intramuscular injection at the dosage of 1.36 to 2.27 mg ceftiofur per pound (3.0 to 5.0 mg/kg) of body weight (1 mL of reconstituted sterile solution per 22 to 37 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days.

Sheep

Administer to sheep by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite).

Goats

Administer to goats by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite). Pharmacokinetic data indicate that elimination of the drug is more rapid in lactating does. For lactating does, the high end of the dose range is recommended.

Horses

Administer to horses by intramuscular injection at the dosage of 1.0 to 2.0 mg ceftiofur per pound (2.2 to 4.4 mg/kg) of body weight (2-4 mL reconstituted sterile solution per 100 lbs body weight). A maximum of 10 mL may be administered per injection site. Treatment should be repeated at 24-hour intervals, continued for 48 hours after clinical signs have disappeared and should not exceed 10 days.

Dogs

Administer to dogs by subcutaneous injection at the dosage of 1.0 mg ceftiofur per pound (2.2 mg/kg) of body weight (0.1 mL reconstituted sterile solution per 5 lbs body weight). Treatment should be repeated at 24-hour intervals for 5-14 days.

Reconstituted NAXCEL Sterile Powder is to be administered to dogs by subcutaneous injection. No vial closure should be entered more than 20 times. Therefore, only the 1 gram vial is approved for use in dogs.

Day-Old Chicks

Administer by subcutaneous injection in the neck region of day-old chicks at the dosage of 0.08 to 0.20 mg ceftiofur/chick. One mL of the 50 mg/mL reconstituted solution will treat approximately 250 to 625 day-old chicks.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only. A sterile 26 gauge needle and syringe or properly cleaned automatic injection machine should be used.

Day-Old Turkey Poults

Administer by subcutaneous injection in the neck region of day-old turkey poults at the dosage of 0.17 to 0.5 mg ceftiofur/poult. One mL of the 50 mg/mL reconstituted solution will treat approximately 100 to 294 day-old turkey poults. Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

CONTRAINDICATIONS

As with all drugs, the use of NAXCEL Sterile Powder is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

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 material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS) or to report any adverse event please call Zoetis Inc. at 1-888-963-8471.

RESIDUE WARNINGS:

Cattle: When used according to label indications, dosage and routes of administration, treated cattle must not be slaughtered for 4 days following the last treatment. When used according to label indications, dosage and routes of administration, a milk discard time is not required. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Swine: When used according to label indications, dosage and route of administration, treated pigs must not be slaughtered for 4 days following the last treatment. **Use of dosages in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.**

Sheep: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Goats: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Horses: Do not use in horses intended for human consumption.

PRECAUTIONS

The effects of ceftiofur on the reproductive performance, pregnancy, and lactation of cattle, swine, sheep, and goats have not been determined.

Cattle

Following subcutaneous administration of ceftiofur sodium in the neck, small areas of discoloration at the site may persist beyond five days, potentially resulting in trim loss of edible tissues at slaughter.

As with any parenteral injection, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Swine

The safety of ceftiofur has not been determined for swine intended for breeding.

Horses

The safety of ceftiofur has not been determined for horses intended for breeding. The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that could be fatal. If acute diarrhea is observed, discontinue use of this antimicrobial and initiate appropriate therapy.

Dogs

The safety of ceftiofur has not been determined for dogs intended for breeding, or pregnant dogs.

ADVERSE REACTIONS

The use of ceftiofur may result in some signs of immediate and transient local pain to the animal.

CLINICAL MICROBIOLOGY

Summaries of MIC data are presented in Tables 1 and 2. Testing followed Clinical and Laboratory Standards Institute (CLSI) Guidelines.

Table 1. Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA

Animal	Organism	Number Tested	Date Tested	MIC_{50}* (μg/mL)	MIC Range (μg/mL)
Bovine	*Mannheimia haemolytica*	461	1988-1992	0.06	≤0.03-0.13
	Mannheimia haemolytica	42	1993	0.015	≤0.003-0.03
	Pasteurella multocida	318	1988-1992	0.06	≤0.03-0.25
	Pasteurella multocida	48	1993	≤0.003	≤0.003-0.015
	Histophilus somni	109	1988-1992	0.06	≤0.03-0.13
	Histophilus somni	59	1993	≤0.0019	no range
	Fusobacterium necrophorum	17	1994	≤0.06	no range
Swine	*Actinobacillus pleuropn.*	83	1993	≤0.03	≤0.03-0.06
	Pasteurella multocida	74	1993	≤0.03	≤0.03-0.06
	Streptococcus suis	94	1993	0.25	≤0.03-1.0
	Salmonella choleraesuis	50	1993	1.0	1.0-2.0
	beta-hemolytic *Streptococcus* spp.	24	1993	≤0.03	≤0.03-0.06
	Actinobacillus suis	77	1998	0.0078	0.0019-0.0078
	Haemophilus parasuis	76	1998	0.06	0.0039-0.25
Sheep	*Mannheimia haemolytica*	39	1992	0.13	≤0.03-0.13
	Pasteurella multocida	23	1992	≤0.03	no range
Canine	*Escherichia coli*	44	1992	4.0	0.06-64.0
	Escherichia coli	18	1990	0.25	0.13-0.5
	Proteus mirabilis	17	1990	≤0.06	≤0.06-0.5
	Proteus mirabilis	23	1992	1.0	≤0.06-4.0
Turkey	*Escherichia coli*	1204	1995	1.0	0.13->32.0

*Minimum inhibitory concentration (MIC) for 90% of the isolates.

Table 2. Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories in the USA and Canada*

Animal	Organism Tested	Number Tested	Date (μg/mL)	MIC_{50}** (μg/mL)	MIC Range
Bovine	*Mannheimia haemolytica*	110	1997-1998	0.06	≤0.03-0.25
	Mannheimia haemolytica	139	1998-1999	≤0.03	≤0.03-0.5
	Mannheimia haemolytica	209	1999-2000	≤0.03	≤0.03-0.12
	Mannheimia haemolytica	189	2000-2001	≤0.03	≤0.03-0.12
	Pasteurella multocida	107	1997-1998	≤0.03	≤0.03-0.25
	Pasteurella multocida	181	1998-1999	≤0.03	≤0.03-0.5
	Pasteurella multocida	208	1999-2000	≤0.03	≤0.03-0.12
	Pasteurella multocida	259	2000-2001	≤0.03	≤0.03-0.12
	Histophilus somni	48	1997-1998	≤0.03	≤0.03-0.25
	Histophilus somni	87	1998-1999	≤0.03	≤0.03-0.125
	Histophilus somni	77	1999-2000	≤0.03	≤0.03-0.06
	Histophilus somni	129	2000-2001	≤0.03	≤0.03-0.12
	Bacteroides fragilis group	29	1994	16.0	≤0.06->16.0
	Bacteroides spp., non-*fragilis* group	12	1994	16.0	0.13->16.0
	Peptostreptococcus anaerobius	12	1994	2.0	0.13-2.0
Swine	*Actinobacillus pleuropn.*	97	1997-1998	≤0.03	no range
	Actinobacillus pleuropn.	111	1998-1999	≤0.03	≤0.03-0.25
	Actinobacillus pleuropn.	126	1999-2000	≤0.03	≤0.03-0.06
	Actinobacillus pleuropn.	89	2000-2001	≤0.03	≤0.03-0.06
	Pasteurella multocida	114	1997-1998	≤0.03	≤0.03-1.0
	Pasteurella multocida	147	1998-1999	≤0.03	≤0.03-0.5
	Pasteurella multocida	173	1999-2000	≤0.03	≤0.03-0.06
	Pasteurella multocida	186	2000-2001	≤0.03	≤0.03-0.12
	Streptococcus suis	106	1997-1998	0.5	≤0.03-4.0
	Streptococcus suis	142	1998-1999	0.25	≤0.03-1.0
	Streptococcus suis	146	1999-2000	0.06	≤0.03-4.0
	Streptococcus suis	167	2000-2001	0.06	≤0.03-4.0
	Salmonella choleraesuis	96	1999-2000	1.0	0.03->4.0
	Salmonella choleraesuis	101	2000-2001	1.0	0.5-2.0
Equine	*Streptococcus equi* subsp. *equi*	12	1994	≤0.0019	no range
	Streptococcus equi subsp. *equi*	29	2002	≤0.03	≤0.03-0.05
	Streptococcus zooepidemicus	48	1994	≤0.0019	no range
	Streptococcus zooepidemicus	59	2002	≤0.03	≤0.03-0.25
	Rhodococcus equi	66	1998	4.0	≤0.03-16.0
	Rhodococcus equi	42	2002	8.0	≤0.03->32.0
	Bacteroides fragilis group	32	1995	>16.0	0.13->16.0
	Bacteroides spp., non-*fragilis* group	12	1995	4.0	0.25-4.0
	Fusobacterium necrophorum	16	1995	≤0.06	no range
Canine	*Escherichia coli*	26	2000	32	0.25->32
	Proteus mirabilis	14	2000	0.25	0.06-0.25
Turkey	*Escherichia coli*	17	1998-1999	1.0	0.25-1.0
	Escherichia coli	25	1999-2000	0.50	0.12-0.5
	Escherichia coli	20	2000-2001	2.0	0.12-16.0
	Citrobacter spp.	37	1995	32.0	0.5->32.0
	Enterobacter spp.	51	1995	>32.0	0.13->32.0
	Klebsiella spp.	100	1995	1.0	0.13-2.0
	Proteus spp.	19	1995	1.0	0.06-32.0
	Pseudomonas spp.***	31	1995	>32.0	0.06->32.0
	Salmonella spp.	24	1995	1.0	0.5-1.0
	Staphylococcus spp. (coagulase positive)	17	1995	2.0	1.0-2.0
	Staphylococcus spp. (coagulase negative)	26	1995	8.0	0.13->32.0
Chicken	*Escherichia coli*	62	1997-1998	0.50	0.25-2.0
	Escherichia coli	53	1998-1999	4.0	0.25->4.0
	Escherichia coli	67	1999-2000	0.50	0.12-16.0
	Escherichia coli	90	2000-2001	1.0	≤0.03-8.0

* The following *in vitro* data are available but their clinical significance is unknown.
** Minimum inhibitory concentration (MIC) for 90% of the isolates.
*** MIC_{50} is 32 μg/mL

PRESCRIBING INFORMATION FOR USE IN SWINE

EXCENEL® RTU EZ

Ceftiofur Hydrochloride

Sterile Suspension

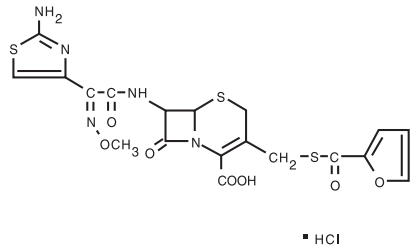
For intramuscular injection in swine.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in swine for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

EXCENEL RTU EZ Sterile Suspension is a ready to use formulation that contains the hydrochloride salt of ceftiofur, which is a broad spectrum cephalosporin antibiotic. Each mL of this ready-to-use sterile suspension contains ceftiofur hydrochloride equivalent to 50 mg ceftiofur, 2.50 mg polyoxyethylene sorbitan monooleate (polysorbate 80), 6.5 mg water for injection in a caprylic/capric triglyceride suspension.

Figure 1. Structure:



• HCl

Chemical Name of Ceftiofur Hydrochloride: 5-Thia-1-azabicyclo[4,2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo-,hydrochloride salt [6R-[6α,7β(Z)]]-

INDICATIONS

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

DOSAGE AND ADMINISTRATION

Shake well before using.

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.

CONTRAINDICATIONS

As with all drugs, the use of EXCENEL RTU EZ Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

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.

RESIDUE WARNINGS:

Injection site volume affects the withdrawal period in swine. When used according to label indications, dosage, and route of administration, treated swine must not be slaughtered for 6 days following the last treatment when injection site volumes are greater than 5 mL up to the maximum injection site volume of 15 mL. When used according to label indications, dosage, and route of administration, treated swine must not be slaughtered for 4 days when injection site volumes are less than or equal to 5 mL. **Do not inject more than 15 mL per injection site.** Use of dosages or injection volumes in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.

PRECAUTIONS

The effects of ceftiofur on swine reproductive performance, pregnancy and lactation have not been determined.

Intramuscular injection in swine can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

CLINICAL PHARMACOLOGY

Ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to swine as either the sodium or hydrochloride salt provides effective concentrations of ceftiofur and desfuroylceftiofur metabolites in plasma above the lowest minimum inhibitory concentration to encompass 90% of the most susceptible isolates (MIC_{90}) for the labeled pathogens: *Actinobacillus pleuropneumoniae, Pasteurella multocida, Streptococcus suis* and *Salmonella* Choleraesuis for the 24 hour period between the dosing intervals. The MIC_{90} for *Salmonella* Choleraesuis (1 µg/mL) is higher than the other three pathogens and plasma concentrations exceed this value for the entire dosing interval only after the 2.27 mg/lb (5 mg/kg) BW dose.

Comparative Bioavailability Summary

The current EXCENEL RTU EZ Sterile Suspension formulation replaces a previously approved formulation. The previously approved EXCENEL RTU EZ product was a reformulation of another ceftiofur hydrochloride injectable product, EXCENEL RTU Sterile Suspension (NADA 140-890). Comparable plasma concentrations of ceftiofur administered as EXCENEL RTU Sterile Suspension or the reformulated EXCENEL RTU EZ Sterile Suspension were demonstrated in a comparative two-treatment, two-period crossover relative bioavailability study in swine. Products were administered via intramuscular (IM) injection into the neck, using alternating sides during periods 1 and 2. A summary of average plasma pharmacokinetic (PK) parameters in swine after a single IM administration of EXCENEL RTU Sterile Suspension and EXCENEL RTU EZ Sterile Suspension at a dose of 2.27 mg CE/lb (5 mg CE/kg) BW is provided in Table 1.

Table 1: Comparative treatment values (arithmetic mean ± SD) for the plasma PK estimates of total ceftiofur (parent compound plus desfuroylceftiofur metabolites) in swine following an IM administration of 2.27 mg CE/lb (5 mg CE/kg) BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	EXCENEL RTU	EXCENEL RTU EZ
C_{max} (µg/mL)	18.2 ± 4.09	19.7 ± 3.39
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	257 ± 57.1	263 ± 54.8
t_{max} (h)	1.5 ± 0.49	1.5 ± 0.73
$t_{1/2}$ (h)	20.0 ± 1.56	20.0 ± 1.82
$t_{>0.2}$ (h)	83.1 ± 10.3	82.5 ± 10.5

C_{max} - maximum plasma concentration
$AUC_{0\text{-}LOQ}$ - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay
t_{max} - the time after initial injection to when C_{max} occurs
$t_{1/2}$ - the plasma half life of the drug
$t_{>0.2}$ - the time plasma concentrations remain above 0.2 µg/mL.

The standard bioequivalence (BE) criteria, based upon the exponentiated 90% confidence bounds about the ratio of treatment means, were met for the pivotal bioequivalence parameters, $AUC_{0\text{-}LOQ}$ and C_{max}, when each formulation was administered to swine IM at a dose rate of 2.27 mg CE/lb (5 mg CE/kg) BW (Table 2).

Table 2: Back-transformed least squares (LS) means and 90% confidence interval (CI) for the two pivotal pharmacokinetic parameters, C_{max} and $AUC_{0\text{-}LOQ}$ in swine following an IM administration of 2.27 mg CE/lb (5 mg CE/kg) BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	LS Mean Difference	90% CI	BE†
C_{max}	1.10	1.03 to 1.18	Yes
$AUC_{0\text{-}LOQ}$	1.03	0.99 to 1.06	Yes

† If the 90% CI of the LS mean difference is within the limits of 0.80 to 1.25, then the results support bioequivalence of treatment groups

In another comparative bioavailability PK study (previously reviewed under NADA 140-890), comparable plasma concentrations of ceftiofur, administered as EXCENEL RTU Sterile Suspension or as NAXCEL Sterile Powder, were demonstrated when each product was administered intramuscularly at the upper end of the label dose range [2.27 mg CE/lb (5 mg CE/kg) BW]. The bioequivalence criteria were met for the $AUC_{0\text{-}LOQ}$, C_{max}, and $t_{>0.2}$ when both products were administered by an intramuscular injection to swine at a dose rate of 5 mg CE/kg BW.

The effectiveness of injection site volumes greater than 5 mL to 15 mL was supported by a comparison of the length of time (hours) that plasma concentrations remained above 0.2 µg/mL ($t_{>0.2}$) between injection site volumes less than or equal to 5 mL and injection site volumes greater than 5 mL to 12 mL. Statistical analysis allowed for an extrapolation of these findings to 15 mL per site. The pharmacokinetic data demonstrated that 5 mg/kg administered IM at injection volumes from greater than 5 mL to 15 mL resulted in acceptable $t_{>0.2}$ for the indication.

MICROBIOLOGY

EXCENEL RTU EZ Sterile Suspension is a ready-to-use formulation that contains the hydrochloride salt of ceftiofur. Ceftiofur is a broad-spectrum cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria. Like other cephalosporins, ceftiofur is predominantly bactericidal *in vitro*, resulting in the inhibition of cell wall synthesis. *In vitro* activity of ceftiofur has been demonstrated against *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Salmonella* Choleraesuis, three pathogens associated with swine respiratory disease. Similarly, *in vitro* activity of ceftiofur has been demonstrated against *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*, the three major pathogens associated with bovine respiratory disease, and against *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, pathogenic anaerobic bacteria associated with bovine foot rot.

Utilizing data that included isolates from swine affected by respiratory disease, zone diameter and minimum inhibitory concentration (MIC) breakpoints were determined using standardized procedures from the Clinical and Laboratory Standards Institute (CLSI, formerly National Committee of Clinical Laboratory Standards) M31-A2. The CLSI-accepted interpretive criteria for ceftiofur against these Gram-negative pathogens are shown in Table 5.

Table 5: CLSI-accepted interpretive criteria for ceftiofur against swine and cattle respiratory pathogens.*

Pathogen	Disk potency	Zone diameter interpretive standards (mm)			MIC breakpoint (µg/mL)		
		S	I	R	S	I	R
Actinobacillus pleuropneumoniae *Pasteurella multocida* *Salmonella* Choleraesuis	30 µg	≥ 21	18 to 20	≤ 17	≤ 2.0	4.0	≥ 8.0
Mannheimia haemolytica *Pasteurella multocida* *Histophilus somni*							
S – Susceptible; I – Intermediate; R – Resistant							

* These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used to determine antimicrobial susceptibility.

EFFECTIVENESS

Plasma concentrations of ceftiofur administered as EXCENEL RTU Sterile Suspension or as EXCENEL RTU EZ Sterile Suspension following intramuscular administration in swine were compared and found to be bioequivalent for $AUC_{0\text{-}LOQ}$ and C_{max}. Therefore, EXCENEL RTU EZ Sterile Suspension has the same effectiveness profile as previously established for EXCENEL RTU Sterile Suspension. Because the effectiveness of cephalosporin antibiotics is dependent upon time above MIC, EXCENEL RTU EZ Sterile Suspension is considered effective for the treatment/control of swine respiratory disease.

ANIMAL SAFETY

Evaluation of target animal safety in swine was based on a PK comparison between the reformulated EXCENEL RTU EZ Sterile Suspension and EXCENEL RTU Sterile Suspension. Ceftiofur administered to swine as the reformulated EXCENEL RTU EZ Sterile Suspension at a dose of 5 mg CE/kg BW by IM injection was demonstrated to be bioequivalent to a corresponding IM injection of EXCENEL RTU Sterile Suspension based upon comparability of their respective $AUC_{0\text{-}LOQ}$ and C_{max} values (see EFFECTIVENESS section). Because of the demonstrated blood level bioequivalence, this study confirms the systemic safety of the reformulated EXCENEL RTU EZ Sterile Suspension in swine when administered by IM injection at a dose of 5 mg CE/kg BW for three consecutive days.

Injection site tissue tolerance and resolution were evaluated after administering EXCENEL RTU EZ Sterile Suspension by intramuscular injection to 8 young pigs with at least the maximum proposed volume of 5 mL per injection site once daily for three consecutive days. Each injection was administered in a different location on the neck, and injection sites alternated between the left and right sides. General health and injection sites were evaluated through 42 days after the first treatment. No test article-related health issues were observed. Mild swelling, erythema, and firmness was observed in a very small number of occasions (≤ 2% of total observations). No swelling was observed from 3 days after the last injection through the end of the study. Grossly visible discoloration of the injection site and histopathologic changes consistent with inflammation were noted in treated pigs necropsied 7 days or 14 days after injection.

A second injection site tissue tolerance study was conducted in 16 adult commercial crossbred pigs to evaluate the administration of EXCENEL RTU EZ Sterile Suspension by intramuscular injection with a maximum dose volume of 15 mL per injection site once daily for three consecutive days. Each injection was administered in a different location on the neck and injection sites alternated between the left and right sides. General health and injection sites were evaluated through 42 days after the first treatment. No test article-related health issues were observed. No swelling, erythema, or firmness were observed during the study. Gross necropsy and histopathologic changes consistent with inflammation were noted in treated pigs necropsied up to 42 days after injection.

TISSUE RESIDUE DEPLETION

Radiolabeled residue metabolism studies established tolerances for ceftiofur residues in swine kidney, liver and muscle. The tolerances for ceftiofur residues are 0.25 ppm in kidney, 3 ppm in liver and 2 ppm in muscle.

A pivotal tissue residue decline study was conducted in swine. In this study, pigs received 2.27 mg of ceftiofur per lb body weight (5 mg of ceftiofur per kg body weight) per day for three consecutive days with an injection volume of 5 mL per site. Ceftiofur residues in edible tissues were less than the tolerances for ceftiofur at 4 days after dosing.

A second pivotal tissue residue decline study was conducted in large swine. In this study, animals received 3 consecutive once daily doses of EXCENEL RTU EZ Sterile Suspension by intramuscular injection at a dose rate of 2.27 mg of ceftiofur per lb body weight (5 mg CFAE/kg BW) with a maximum injection volume of 15 mL per injection site. Ceftiofur residues in tissues were below the tolerance in kidney by 6 days after dosing.

Collectively, the data from these two studies support a 4-day pre-slaughter withdrawal period in swine receiving injection site volumes less than or equal to 5 mL and a 6-day withdrawal period when receiving injection site volumes greater than 5 mL up to 15 mL per injection site.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted 15° to 40°C (59° to 104°F). Protect from freezing. Shake well before using. Contents should be used within 42 days after the first dose is removed.

HOW SUPPLIED

EXCENEL RTU EZ Sterile Suspension is available in 100 mL and 250 mL vials.

Approved by FDA under NADA # 141-288

Revised: March 2019

40013918A&P

zoetis
Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Draxxin® 25
(tulathromycin injection) Injectable Solution

Antibiotic
25 mg of tulathromycin/mL
For use in suckling calves, dairy calves, veal calves, and swine. Not for use in ruminating cattle.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
DRAXXIN 25 Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of DRAXXIN 25 contains 25 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monothioglycerol (5 mg/mL), citric acid (4.8 mg/mL) with hydrochloric acid and sodium hydroxide added to adjust pH. DRAXXIN 25 consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio.

The chemical names of the isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino) methyl]-α-L-ribohexopyrano-syl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribohexopyrano-syl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylohexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS
Swine
DRAXXIN 25 Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis,* and *Mycoplasma hyopneumoniae*; and for the control of SRD associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida,* and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed.

Suckling Calves, Dairy Calves, and Veal Calves
BRD - DRAXXIN 25 Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*.

DOSAGE AND ADMINISTRATION
Swine
Inject intramuscularly as a single dose in the neck at a dosage of 2.5 mg/kg (1 mL/22 lb) Body Weight (BW). Do not inject more than 4 mL per injection site.

Table 1. DRAXXIN 25 Swine Dosing Guide (25 mg/mL)

Animal Weight (Pounds)	Dose Volume (mL)
4	0.2
10	0.5
15	0.7
20	0.9
22	1.0
25	1.1
30	1.4
50	2.3
70	3.2
90	4.0

Calves
Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1 mL/22 lb) body weight (BW). Do not inject more than 11.5 mL per injection site.

Table 2. DRAXXIN 25 Calf Dosing Guide (25 mg/mL)

Animal Weight (Pounds)	Dose Volume (mL)
50	2.3
75	3.4
100	4.5
150	7.0
200	9.0
250	11.5

CONTRAINDICATIONS
The use of DRAXXIN 25 Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS
FOR USE IN ANIMALS ONLY.
NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.
NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS
Swine
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.
Calves
Calves intended for human consumption must not be slaughtered within 22 days from the last treatment with DRAXXIN 25 Injectable Solution. This drug is not for use in ruminating cattle.

PRECAUTIONS
Swine
The effects of Draxxin 25 Injectable Solution on porcine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.
Cattle
The effects of Draxxin 25 Injectable Solution on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS
Swine
In one field study, one out of 40 pigs treated with DRAXXIN Injectable Solution (100 mg/mL) at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.
Calves
In one BRD field study, two calves treated with DRAXXIN Injectable Solution (100 mg/mL) at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

Post Approval Experience
The following adverse events are based on post approval adverse drug experience reporting for DRAXXIN Injectable Solution (100 mg/mL). Not all adverse events are reported to the FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions. For a complete listing of adverse reactions for DRAXXIN Injectable Solution or DRAXXIN 25 Injectable Solution reported to the CVM see: http://www.fda.gov/AnimalVeterinary.

CLINICAL PHARMACOLOGY
At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than lipophilic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.[1] Markedly higher tulathromycin concentrations are observed in the lung parenchyma as compared to the plasma, and these elevated concentrations can remain in lung tissue for several days beyond that which can be measured in the plasma. However the clinical relevance of these elevated lung concentrations is undetermined.

As a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] When acting as a cidal compound, they tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration.[3] Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

[1] Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis., **27**:28-32.
[2] Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., **16**:438-443.
[3] Andes D, Anon J, Jacobs MR, Craig WA. (2004). Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections. Clin Lab Med., **24**:477-502.

Swine
Following intramuscular (IM) administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is nearly completely absorbed, with peak plasma concentrations achieved within ~0.25 hr. The volume of distribution exceeds 15 L/kg, which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half- life (60 to 90 hours) despite a rapid systemic free drug clearance (187 mL/kg/hr). There are no gender differences in swine tulathromycin pharmacokinetics.

Comparative Bioavailability Summary
Despite slightly lower peak concentrations with DRAXXIN 25 Injectable Solution, a single IM dose of 2.5 mg tulathromycin/kg BW of either DRAXXIN Injectable Solution (100 mg/mL) or DRAXXIN 25 Injectable Solution (25 mg/mL) resulted in comparable tulathromycin total systemic exposure. Therefore, DRAXXIN 25 Injectable Solution is considered to be therapeutically equivalent to DRAXXIN Injectable Solution when administered to swine by IM injection at a dose of 2.5 mg tulathromycin/kg BW.

Calves
Following subcutaneous (SC) administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is nearly completely absorbed, with peak plasma concentrations achieved within ~0.25 hr. The volume of distribution exceeds 11 L/kg[4], which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half- life of more than 100 hours, despite a rapid systemic free drug clearance (170 mL/kg/hr). No pharmacokinetic differences are observed in castrated male versus female calves.

Comparative Bioavailability Summary
Despite lower peak concentrations with DRAXXIN 25 Injectable Solution, a single SC dose of 2.5 mg tulathromycin/kg BW of either DRAXXIN Injectable Solution (100 mg/mL) or DRAXXIN 25 Injectable Solution (25 mg/mL) resulted in comparable total systemic tulathromycin exposure. Therefore, DRAXXIN 25 Injectable Solution is considered to be therapeutically equivalent to DRAXXIN Injectable Solution when administered to calves by SC injection at a dose of 2.5 mg tulathromycin/kg BW.
[4] Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.

MICROBIOLOGY
Swine
Tulathromycin has demonstrated *in vitro* activity against *A. pleuropneumoniae*, *P. multocida, B. bronchiseptica, H. parasuis*, and *M. hyopneumoniae*. The MICs of tulathromycin against indicated pathogens collected from field studies were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A and M31-A3). MICs for *H. parasuis* were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a CO2-enriched atmosphere. These values are represented in Table 3, below.

Table 3. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating SRD in the U.S. and Canada.

Indicated pathogen	Date isolated	No. of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuropneumoniae	2000-2002 2007-2008	135 88	16 16	32 16	16 to 32 4 to 32
Haemophilus parasuis	2000-2002	31	1	2	0.25 to > 64
Pasteurella multocida	2000-2002 2007-2008	55 40	1 1	2 2	0.5 to> 64 ≤ 0.03 to 2
Bordetella bronchiseptica	2000-2002	42	4	8	2 to 8

*The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Calves
Tulathromycin has demonstrated *in vitro* activity against *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*, four pathogens associated with BRD. The MICs of tulathromycin against indicated pathogens collected from field studies using DRAXXIN Injectable Solution (100 mg/mL) were determined using methods recommended by the CLSI (M31-A2). These values are represented in Table 4, below.

Table 4. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD in the U.S.

Indicated pathogen	Date isolated	No. of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1999	642	2	2	0.5 to 64
Pasteurella multocida	1999	221	0.5	1	0.25 to 64
Histophilus somni	1999	36	4	4	1 to 4
Mycoplasma bovis	1999	43	0.125	1	≤ 0.063 to > 64

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS

Swine

Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore effectiveness studies conducted with DRAXXIN Injectable Solution (100 mg/mL) support the effectiveness for DRAXXIN 25 Injectable Solution.

In a multi-location field study to evaluate the treatment of naturally occurring SRD, 266 pigs were treated with DRAXXIN Injectable Solution (100 mg/mL). Responses to treatment were compared to saline-treated controls. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F on Day 7. The treatment success rate was significantly greater ($P \leq 0.05$) in DRAXXIN-treated pigs (70.5%) compared to saline-treated pigs (46.1%). *M. hyopneumoniae* was isolated from 106 saline-treated and non-treated sentinel pigs in this study.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN Injectable Solution (100 mg/mL) against *M. hyopneumoniae*. Ten days after inoculation intranasally and intratracheally with a field strain of *M. hyopneumoniae*, 144 pigs were treated with either DRAXXIN (2.5 mg/kg BW) intramuscularly or an equivalent volume of saline. Pigs were euthanized and necropsied 10 days post-treatment. The mean percentage of gross pneumonic lung lesions was statistically significantly lower ($P < 0.0001$) for DRAXXIN-treated pigs than for saline-treated pigs in both studies (8.52% vs. 23.62% and 11.31% vs. 26.42%).

The effectiveness of DRAXXIN Injectable Solution (100 mg/mL) for the control of SRD was evaluated in a multi-location natural infection field study. When at least 15% of the study candidates showed clinical signs of SRD, all pigs were enrolled and treated with DRAXXIN (226 pigs) or saline (227 pigs). Responses to treatment were evaluated on Day 7. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F. The treatment success rate was significantly greater ($P < 0.05$) in DRAXXIN-treated pigs compared to saline-treated pigs (59.2% vs. 41.2%).

Calves

Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore effectiveness studies conducted with DRAXXIN Injectable Solution (100 mg/mL) support the effectiveness for DRAXXIN 25 Injectable Solution.

BRD - In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN Injectable Solution (100 mg/mL). Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. The cure rate was significantly higher ($P \leq 0.05$) in DRAXXIN-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the DRAXXIN-treated calves compared to nine BRD-related deaths in the saline-treated calves.

Fifty-two DRAXXIN Injectable Solution (100 mg/mL)-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs. Of the 52 DRAXXIN-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.

A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with DRAXXIN Injectable Solution (100 mg/mL) to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with DRAXXIN. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of DRAXXIN Injectable Solution (100 mg/mL) in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves. As a result, DRAXXIN Injectable Solution (100 mg/mL) was considered effective for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni,* and *M. bovis* in suckling calves, dairy calves, and veal calves.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN Injectable Solution (100 mg/mL) against *Mycoplasma bovis*. A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis*. When calves became pyrexic and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the DRAXXIN-treated calves compared with saline-treated calves (11.3% vs. 28.9%, $P = 0.0001$ and 15.0% vs. 30.7%, $P < 0.0001$).

ANIMAL SAFETY

Swine

Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore systemic target animal safety studies conducted with DRAXXIN Injectable Solution support the systemic safety for DRAXXIN 25 Injectable Solution.

Safety studies were conducted in pigs receiving a single intramuscular dose of 25 mg/kg BW, or 3 weekly intramuscular doses of 2.5, 7.5, or 12.5 mg/kg BW (both studies utilized DRAXXIN Injectable Solution (100 mg/mL)). In all groups, transient indications of pain after injection were seen, including restlessness and excessive vocalization. Tremors occurred briefly in one animal receiving 7.5 mg/ kg BW. Discoloration and edema of injection site tissues and corresponding histopathologic changes were seen in animals at all dosages and resolved over time. No other drug-related lesions were observed macroscopically or microscopically.

Sixteen growing pigs were injected with either saline or DRAXXIN 25 Injectable Solution as a single injection of 4 mL. Injection site observations included two instances of erythema in the DRAXXIN 25-treated group on Day 1 post-injection. No heat, sensitivity, firmness, necrosis, drainage, or swelling was observed at any injection sites in either treatment group. The gross and microscopic findings in the DRAXXIN 25-treated group were consistent with inflammatory changes induced by injections and were considered to be mild or moderate with progression to macroscopic resolution by Day 28 post-injection and microscopic resolution by Day 42 post-injection.

Calves

Plasma concentrations of tulathromycin administered as DRAXXIN Injectable Solution (100 mg/mL) or as DRAXXIN 25 Injectable Solution were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore effectiveness studies conducted with DRAXXIN Injectable Solution support the systemic safety for DRAXXIN 25 Injectable Solution.

A safety study was conducted in feeder calves receiving DRAXXIN Injectable Solution (100 mg/mL) as a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histopathologic changes were seen in animals in all dosage groups. These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically.

An exploratory study was conducted in feeder calves receiving DRAXXIN Injectable Solution (100 mg/mL) as a single subcutaneous dose of 10, 12.5, or 15 mg/kg BW. Macroscopically, no lesions were observed. Microscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW and two of six calves administered 15 mg/kg BW.

A safety study was conducted in preruminant calves 13 to 27 days of age receiving DRAXXIN Injectable Solution (100 mg/mL) at 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

Sixteen growing cattle were injected with either saline (eight animals) as a single injection of 11.5 mL or DRAXXIN 25 Injectable Solution (eight animals) as a single injection of either 2.5 mg/kg BW or a dose volume of 11.5 mL (whichever volume was higher). One calf in the DRAXXIN 25-treated group was observed to have firmness at the injection site for a single day. Two DRAXXIN 25-treated calves exhibited injection site swelling. In one calf, the swelling resolved within 48 hours. In the other calf, the swelling was observed over a three-day period, after which the calf underwent a scheduled necropsy, preventing further injection site observations. No injection site swelling was observed in saline-treated animals. At necropsy, three of the saline-treated calves and five of the DRAXXIN 25-treated calves had altered tissue present at the injection site. The gross and microscopic findings in the DRAXXIN 25-treated group were consistent with inflammatory changes induced by injections, were considered to be mild to marked, and progressed to macroscopic resolution and microscopic resolution by Day 42 post-injection.

STORAGE CONDITIONS:

Store at or below 25°C (77°F). Use within 90 days of first vial puncture.

HOW SUPPLIED

DRAXXIN 25 Injectable Solution is available in the following package sizes:
50 mL vial
100 mL vial
250 mL vial

Approved by FDA under # NADA 141-349

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

To report a suspected adverse reaction or to request a safety data sheet 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.

For additional DRAXXIN 25 product information call: **1-888-DRAXXIN** or go to **www.DRAXXIN.com**

4019203A&P
Revised: March 2019

EXCEDE® FOR SWINE

(Ceftiofur Crystalline Free Acid)

Sterile Suspension 100 mg/mL

For intramuscular administration in the post-auricular region of the neck of swine.

CAUTION

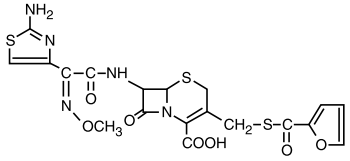
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal Law prohibits extra-label use of this drug in swine for disease prevention purposes; at unapproved doses; frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including ß-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 100 mg ceftiofur, in a Miglyol® and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:



Chemical name of ceftiofur crystalline free acid:
7-[[2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetyl]amino]-3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

INDICATIONS

EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis,* and *Streptococcus suis;* and for the control of SRD associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis,* and *Streptococcus suis* in groups of pigs where SRD has been diagnosed.

DOSAGE

Administer by intramuscular (IM) injection in the post-auricular region of the neck as a single dosage of 2.27 mg ceftiofur equivalents (CE)/lb (5.0 mg CE/kg) body weight (BW). This is equivalent to 1 mL sterile suspension per 44 lb (20 kg) BW. No more than 2 mL should be injected in a single injection site. Injection volumes in excess of 2 mL per injection site may result in violative residues. Pigs heavier than 88 lb (40 kg) will require more than one injection.

Most animals will respond to treatment within three to five days. If no improvement is observed, the diagnosis should be re-evaluated.

ADMINISTRATION

Shake well before using. EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is to be administered by intramuscular injection in the post-auricular region of the neck.

CONTRAINDICATIONS

As with all drugs, the use of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

FOR USE IN ANIMALS ONLY.
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. Sensitization of the skin may be avoided by wearing protective gloves.

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 material safety data sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information or to obtain a material safety data sheet, call 1-888-963-8471.

RESIDUE WARNINGS

- A maximum of 2 mL of formulation should be injected at each injection site. Injection volumes in excess of 2 mL per injection site may result in violative residues.
- Following label use as a single treatment, a 14-day pre-slaughter withdrawal period is required.
- **Use of dosages in excess of 5.0 mg ceftiofur equivalents (CE)/kg or administration by an unapproved route may result in illegal residues in edible tissues.**

PRECAUTIONS

The safety of ceftiofur has not been demonstrated for pregnant swine or swine intended for breeding.

Administration of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL as directed may induce a transient reaction at the site of injection and underlying tissues that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS

An injection site tolerance study demonstrated that EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is well tolerated in pigs. Half of the injection sites at both 3 and 7 days post-injection were scored as "negative" for irritation and the other half were scored as "slight irritation". All gross observations and measurements of injection sites qualified the sites at 10 days post-injection as "negative" for irritation.

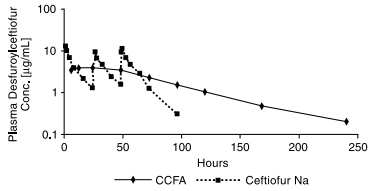
No adverse effects were observed in multi-location field efficacy studies involving more than 1000 pigs.

CLINICAL PHARMACOLOGY

Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder), ceftiofur hydrochloride (EXCENEL® RTU Sterile Suspension) or ceftiofur crystalline free acid (EXCEDE FOR SWINE Sterile Suspension 100 mg/mL) is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to swine as ceftiofur crystalline free acid (CCFA) at a single IM dosage of 2.27 mg CE/lb (5.0 mg CE/kg) BW provides concentrations of ceftiofur and desfuroylceftiofurrelated metabolites in plasma that are multiples above the MIC_{90}* for the SRD label pathogens *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis* and *Streptococcus suis* for an extended period of time (see Figure 2 and Tables 1–2).

The average plasma concentrations of ceftiofur- and desfuroylceftiofur-related metabolites for CCFA (EXCEDE FOR SWINE Sterile Suspension 100 mg/mL) after IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW and those for ceftiofur sodium (NAXCEL Sterile Powder) after IM administration at 1.36 mg CE/lb (3 mg CE/kg) BW for three consecutive days are presented in Figure 2 below.

Figure 2. Average plasma concentrations of ceftiofur- and desfuroylceftiofur-related metabolites for CCFA (EXCEDE FOR SWINE Sterile Suspension 100 mg/mL) after IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW and those for ceftiofur sodium (NAXCEL Sterile Powder) after IM administration at 1.36 mg CE/lb (3 mg CE/kg) BW for three consecutive days



Pharmacokinetic parameters measured after a single IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL in the post-auricular region of the neck of swine are presented in the following table (Table 1).

* Minimum inhibitory concentration for 90% of the isolates

Table 1. Pharmacokinetic parameters in swine after a single IM administration of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL at 2.27 mg CE/lb (5.0 mg CE/kg) BW

Pharmacokinetic Parameter	Mean Value ± Standard Deviation (non-compartmental analyses)
C_{max} (µg/mL)	4.17 ± 0.92
t_{max} (h)	22.0 ± 12.2
$AUC_{0\text{-}LOQ}$ (µg•h/mL)	373.0 ± 56.1
$t_{1/2}$ (h)	49.6 ± 11.8

C_{max} = maximum plasma concentration (in µg CE/mL)
t_{max} = the time after injection when C_{max} occurs (in hours)
$AUC_{0\text{-}LOQ}$ = the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg CE/mL)
$t_{1/2}$ = terminal phase biological half-life (in hours)

Table 2. Ceftiofur minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from SRD treatment and control field studies conducted in the U.S.

Indicated Pathogens	Year(s) of Isolation	Field Study	Number of Isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Actinobacillus pleuropneumoniae	2000 to 2001	Treatment	5	NA	NA	≤0.03 to 0.06
	2009	Control	34	0.03	0.06	0.015 to 0.06
Pasteurella multocida	2000 to 2001	Treatment	20	≤0.03	≤0.03	≤0.03†
	2009	Control	67	≤0.004	≤0.004	≤0.004†
Streptococcus suis	2000 to 2001	Treatment	30	0.06	0.12	≤0.03 to 0.5
	2009	Control	141	0.25	1	0.03 to >2

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.
† No range; all isolates yielded the same value.

MICROBIOLOGY

Ceftiofur has demonstrated *in vitro* activity against *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis,* and *Streptococcus suis,* four major pathogenic bacteria associated with SRD.

The minimum inhibitory concentrations (MICs) of ceftiofur against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI) using the M31-A and M31-A3 standards for the SRD treatment (2000-2001) and control (2009) studies, respectively. Isolates from the SRD treatment study were obtained from lung tissue collected from non-treated pigs prior to enrollment and saline-treated pigs that died or were euthanized during the study. Isolates from the SRD control study were obtained from lung tissue from non-treated pigs euthanized prior to enrollment and from saline- and ceftiofur-treated pigs that died or were euthanized during the study. The susceptibility results for the treatment and control studies are presented in Table 2.

Based on pharmacokinetic data from studies of ceftiofur in swine after a single intramuscular injection of 2.27 mg CE/lb (5.0 mg CE/kg) BW, the following interpretive criteria are recommended by CLSI:

Table 3. CLSI-accepted interpretive criteria for ceftiofur against swine respiratory disease pathogens*

Pathogens	Disk Potency	Zone Diameter (mm)	MIC (µg/mL)	Interpretation
Actinobacillus pleuropneumoniae	30 µg	≥21	≤2.0	(S) Susceptible
Pasteurella multocida		18-20	4.0	(I) Intermediate
Streptococcus suis		≤17	≥8.0	(R) Resistant

* These interpretive criteria should only be used when the CLSI M31-A3 performance standard is used to determine antimicrobial susceptibility to ceftiofur.

EFFECTIVENESS

The effectiveness of a single dose of 2.27 or 3.18 mg CE/lb BW (5.0 or 7.0 mg CE/kg BW) EXCEDE FOR SWINE Sterile Suspension 100 mg/mL for the treatment of SRD was confirmed in a well-controlled, multi-location field study. A total of 706 pigs with clinical signs of bacterial respiratory disease were enrolled and treated with a placebo injection or EXCEDE FOR SWINE Sterile Suspension 100 mg/mL administered as a single IM injection in the post-auricular region of the neck. Clinical observations were performed on Days 1-7 and rectal temperatures were taken on Days 1, 3, and 6 following treatment (Day 0). Necropsies were performed on all pigs that died during the study and after euthanasia of all remaining study pigs at the end of the 14-day post-enrollment study period. Lung lesions were scored and lungs were submitted for bacterial identification. Mortality rates were numerically lower (but not statistically different) for the EXCEDE FOR SWINE Sterile Suspension 100 mg/mL-treated groups (4.3% for the 5.0 mg CE/kg BW group and 4.2% for the 7.0 mg CE/kg BW group) compared with the placebo-treated control group (6.3%). There was a statistically significant ($p<0.05$) improvement in clinical cure rates for the EXCEDE FOR SWINE Sterile Suspension 100 mg/mL-treated groups (24.8% for the 5.0 mg CE/kg BW group and 26.4% for the 7.0 mg CE/kg BW group) compared with the placebo-treated control group (17.7%). Lung lesion scores were numerically higher (but not statistically different) for the EXCEDE FOR SWINE Sterile Suspension 100 mg/mL-treated groups (10.4% for both the 5.0 mg CE/kg BW and the 7.0 mg CE/kg BW group) compared with the placebo-treated control group (9.2%). Bacteriological culture of the lungs of study pigs identified the following respiratory pathogens: *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis,* and *Streptococcus suis.*

The effectiveness of a single dose of 2.27 CE/lb BW (5.0 mg CE/kg BW) EXCEDE FOR SWINE for the control of SRD was evaluated in a multi-location natural infection field study. At each site, when at least 15% of the study candidates in a pen showed clinical signs of SRD, all pigs in the pen were enrolled and treated with EXCEDE FOR SWINE ($n = 346$) or saline ($n = 347$). Responses to treatment were evaluated 7 days post-treatment. Success was defined as a pig that survived to Day 7 and had normal attitude, normal respiration, and a rectal temperature of < 104 °F. The treatment success rate was significantly higher ($p = 0.0188$) for EXCEDE FOR SWINE-treated pigs (59.6%) compared to the saline-treated pigs (41.4%). Bacteriological culture of the lungs of study pigs identified the following respiratory pathogens: *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis,* and *Streptococcus suis.*

Table 4. Acceptable quality control ranges for ceftiofur against CLSI recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC No.)	MIC (µg/mL)	Zone Diameter, mm (Disk Content 30 µg)
E. coli ATCC 25922	0.25–1.0	26–31
S. aureus ATCC 29213	0.25–1.0	—
S. aureus ATCC 25923	—	27–31
P. aeruginosa ATCC 27853	16.0–64.0	14–18

ANIMAL SAFETY

After parenteral administration, CCFA, ceftiofur sodium, and ceftiofur hydrochloride are metabolized to the same principal metabolite, desfuroylceftiofur. Plasma levels achieved are similar after recommended dosing (Figure 2). Therefore, studies conducted with ceftiofur sodium are adequate to evaluate the systemic safety of CCFA. Results from a five-day tolerance study in normal feeder pigs indicated that ceftiofur sodium produced no overt adverse signs of toxicity and was well tolerated when administered at 57 mg CE/lb (125 mg/kg) BW (more than 25 times the recommended dosage of CCFA) for five consecutive days. An additional dose toxicity study was conducted to determine the safety margin of ceftiofur in swine. Five barrows and five gilts per group were administered ceftiofur sodium IM at 0, 2.27, 6.81 and 11.36 mg CE/lb (0, 5, 15, 25 mg CE/kg) BW (0, 1, 3 and 5 times the recommended dosage for CCFA) for 15 consecutive days. There were no adverse systemic effects observed, indicating that ceftiofur sodium has a wide margin of safety when administered intramuscularly in feeder pigs.

A separate study evaluated the injection site tissue tolerance of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL in swine when administered intramuscularly as a single injection at the maximum recommended dose volume of 2 mL (approximately 5 mg CE/kg BW) per injection site. Because injection site volumes greater than 2 mL may result in violative residues, only injection volumes of 2 mL were evaluated in this study. EXCEDE FOR SWINE Sterile Suspension 100 mg/mL was injected intramuscularly into each side of the neck of six swine at a dose volume of 2 mL/injection site. Clinical observations were made daily. At 3, 7 and 10 days post-injection, pairs of animals were euthanized and the neck injection sites were dissected for pathological examination (4 injection sites per time point). The injections were well tolerated in all pigs. Clinically, injection site reactions ranged from nondetectable (6 of 12 sites) to a transitory (up to 4 days post-injection) palpable, nonvisible swelling (2 of 12 sites) or a small, visible, reddened nodule at the needle insertion point (4 of 12 sites; 3 of 4 nodules were barely detectable by 3 to 7 days post-injection). There was no clinical evidence of the injections at 10 days post-injection. At necropsy, half of the injection sites at both 3 and 7 days post-injection were scored as “negative” for irritation and the other half were scored as “slight irritation”. One animal had a visible lesion described as an area of tan with red speckles present in the deep muscle fascia, less than 6 cm^2, at 10 days post-injection; this lesion and the remaining injection sites evaluated at 10 days post-injection were scored as “negative” for irritation.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F). Shake well before using. Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is available in the following package size:
100 mL vial

NADA #141-235, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

www.excede.com or call
1-888-963-8471

Revised: November 2013

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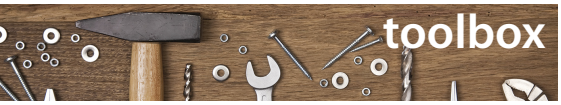

Toolbox is a series of interviews with veterinarians about their experiences managing antimicrobials, vaccines and other tools for swine health. It is produced by the editors of *Pig Health Today*® on behalf of the US Pork Business of Zoetis.

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