CEFTIFLEX- ceftiofur sodium injection, powder, for solution
Cephazone Pharma LLC

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.

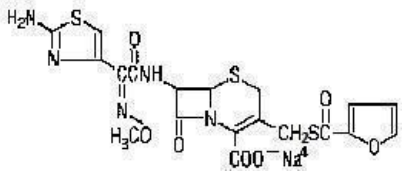
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Approved by FDA under ANADA # 200-420

Ceftiofur Sodium 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-carboxylic acid, 7-[[(2-amino-4-thiazoly)(methoxyimino)-acetyl]amino]-3-[[(2-furanylcarbonyl)thio] methyl]-8-oxo-, monosodium salt, [6R-[6α,7β(Z)]]-

RECONSTITUTION OF THE STERILE POWDER:

Ceftiofur Sodium 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

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

Swine

Ceftiofur Sodium 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

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

Goat

Ceftiofur Sodium Sterile Powder is indicated for treatment of caprine respiratory disease

(goat pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Horses

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

Dogs

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

Day-Old Chicks

Ceftiofur Sodium 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

Ceftiofur Sodium 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 judgment 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 judgment 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 judgment 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 Ceftiofur Sodium 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 Ceftiofur Sodium 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 Ceftiofur Sodium Sterile Powder is to be administered by subcutaneous injection only.

CONTRAINDICATIONS:

As with all drugs, the use of Ceftiofur Sodium 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.

CONTACT INFORMATION:
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Cephazone at (800) 587-4306. 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/reportanimalae

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 sign of immediate and transient local pain to the animal.

CLINCAL 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_{90}(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	1088-1992	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
	β-hemolyticStreptococcus 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	Number Tested	Date Tested	MIC_{90}(µg/mL)**	MIC Range (µg/mL)

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
	Peptostreptocuccus 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	0.50	≤ 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 -0.5
	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	≤ 0.03 ->16.0
	Bacteroides spp. nonfragilis group	12	1995	4.0	0.25 - 4.0
	Fusobacterium necrophorum	16	1995	≤ 0.06	No range
Canine	*Escherichia coli*	26	2000	32.00	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	0.25-1.0
	Escherichia coli	20	2000-20001	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 negative)	17	1995	2.0	1.0 – 2.0
	Staphylococcus spp.(coagulase positive)	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	2000-20001	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

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW

(swine) or 0.5 to 1.0 mg ceftiofur equivalents/ lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 ug) diffusion data, the following breakpoints are recommended by CLSI.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Based on the pharmacokinetic studies of ceftiofur in horses after a single intramuscular injection of 1 mg ceftiofur equivalents/lb (2.2 mg/kg) BW, clinical effectiveness data and MIC data, the following breakpoint is recommended by CLSI.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 22	≤ 0.25	(S) Susceptible

The susceptible only category is used for populations of organisms (usually one species) for which regression analysis (disk vs. MIC) cannot be performed. These breakpoints will permit detection of strains with decreased susceptibility as compared to the original population.

Standardized procedures require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain. Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts.

Table 3. Acceptable quality control ranges for ceftiofur against National Committee for Clinical and Laboratory Standards Institute recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC Number)	Zone Diameter* (mm)	MIC Range (µg/mL)
Escherichia coli (25922)	26-31	0.25-1.0
Staphylococcus aureus (29213)	-	0.25-1.0
Staphylococcus aureus (25923)	27-31	-
Pseudomonas aeruginosa (27853)	14-18	16.0-64.0
Actinobacillus pleuropneumoniae (27090)	34-42**	0.004-0.015***
Histophilus somni (700025)	36-46**	0.0005-0.004***

*All testing performed using a 30 µg disk.

** Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller-Hinton agar, incubated in 5-7% CO2 for 20-24 hours.

*** MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using

Veterinary fastidious medium (VFM).

HOW SUPPLIED:

Ceftiofur Sodium Sterile Powder is available in the following package sizes:

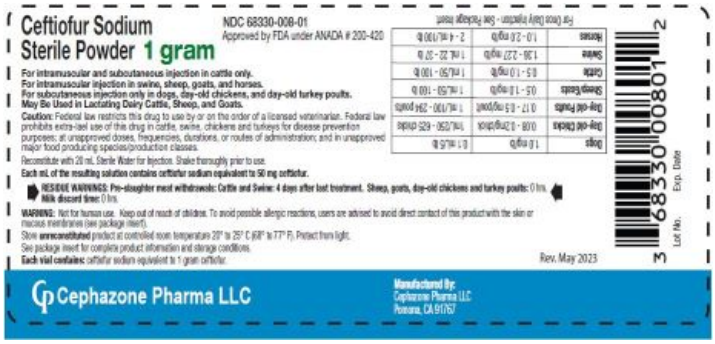
1 gram vial

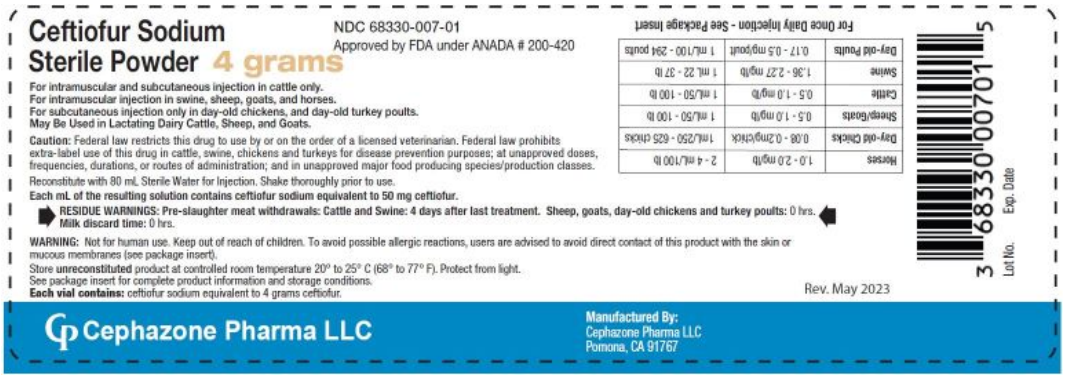
4 gram vial

1. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard - Second Edition. NCCLS document M31-A2. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

Manufactured by:
Cephzaone Pharma LLC
Pomona, CA 91767

Rev. July 2023





CEFTIFLEX

ceftiofur sodium injection, powder, for solution

Product Information			
Product Type	PRESCRIPTION ANIMAL DRUG	**Item Code (Source)**	NDC:68330-008
Route of Administration	INTRAMUSCULAR, SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CEFTIOFUR SODIUM (UNII: NHI34IS56E) (CEFTIOFUR - UNII:83JL932I1C)	CEFTIOFUR SODIUM	50 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68330-008-01	12 in 1 CARTON		
1		1 in 1 BOX		
1		20 mL in 1 VIAL, GLASS		
2	NDC:68330-008-02	6 in 1 CARTON		
2		1 in 1 BOX		
2		80 mL in 1 VIAL, GLASS		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANADA	ANADA200420	07/15/2009	

Labeler - Cephazone Pharma LLC (138954909)

Registrant - Cephazone Pharma LLC (138954909)

Establishment			
Name	**Address**	**ID/FEI**	**Business Operations**
Cephazone Pharma LLC		138954909	manufacture

Establishment			
Name	**Address**	**ID/FEI**	**Business Operations**
Orchid Pharma Limited		675829201	api manufacture