Vétoquinol

4650 '01 MAR 21 A10:41

March 1, 2001

Dr. Lonnie Luther
Quality Assurance Support Team (HFV-102) Room 387
FDA Center for Veterinary Medicine
7500 Standish Place
Rockville, MD 20855

Dear Dr. Luther,

Please find enclosed a suitability petition submitted on behalf of Vetoquinol, N.-A. Inc. of Canada. Vétoquinol requests consideration of this suitability petition to file an ANADA for Cefadroxil Oral Paste.

Please call if you have questions.

Sincerely,

RECEIVED
MAR 15 2001
BY:

Pierre Gadbois d.m.v.
Manager, Regulatory Affairs – Vétoquinol N.-A. Inc.

OIP-0140

CP1

Vétoquinol N.-A. Inc. - 2000, chemin Georges, Lavaltrie (Quebec) Canada J0K 1H0
Tel.: (450) 586-2252 - Fax: (450) 586-4649 - www.vetoquinol.ca

SUITABILITY PETITION

IDENTIFICATION OF PETITIONER:

This Suitability Petition is submitted on behalf of Vétoquinol N.-A., Inc. of Canada under Section 512 (n)(3) of the Federal Food, Drug, and Cosmetic Act.

ACTION REQUESTED:

The petitioner requests permission from the Commissioner to file an Abbreviated New Animal Drug Application (ANADA) for a different dosage form of an approved pioneer product. The pioneer product is Fort Dodge Animal Health's CEFA-DROPS® Cefadroxil-Powder for Oral Suspension, approved by the Food and Drug Administration under NADA 140-684. Cefadroxil is a semi-synthetic cephalosporin antibiotic approved for use in dogs and cats. A copy of the pioneer product labeling (package insert) is included (Attachment 1).

The ANADA will provide for the use of an oral paste dosage form for administration to dogs and cats rather than the oral suspension form of the pioneer product. The product will be formulated to contain cefadroxil monohydrate equivalent to 20 mg or 100 mg cefadroxil per mL of a palatable paste in an oil base. The pioneer product is formulated to contain cefadroxil monohydrate equivalent to 50 mg of cefadroxil per mL when reconstituted according to label directions. Both the proposed and pioneer products are administered to affected animals at the rate of 10 mg/lb of body weight twice daily (dogs) and 10 mg per pound of body weight administered once daily (cats).

The product labeling will provide for indications, recommended dosages, contraindications, precautions and warnings identical to the pioneer product. Draft labeling for the proposed product is provided (Attachment II).

The proposed product label will differ from the pioneer product specifically as follows:

1. Labeled as "Oral Paste" rather than "Powder for Oral Suspension".
2. Contents are labeled as cefadroxil per mL of paste rather than per container.
3. The **Dosage Administration** instructions will be revised to describe delivery of the paste drug product using a HDPE syringe with an adjustable ring to deliver the desired dose.
4. It is anticipated that stability studies will support storage of the generic product at room temperature conditions.
5. The net contents of the containers are yet to be determined.

STATEMENT OF GROUNDS:

The proposed product contains the same active ingredient and will be labeled with the same indications, recommended dose rates, contraindications, precautions and warnings as the approved pioneer product. Because of oral administration and absorption after the cefadroxil is dissolved in the stomach, the clinical effect for both drugs is expected to be similar. The sponsor intends to provide results of blood level bioequivalency testing to demonstrate efficacy and safety of the product as well as palatability information for the product.

ENVIRONMENTAL IMPACT:

The action of submitting this Suitability Petition and its review by the FDA - Center for Veterinary Medicine is not expected to have an environmental impact. The action requested qualifies for categorical exclusion under 21 CFR Part 25.30(h) from the requirement for an environmental assessment and, to the best of the sponsor's knowledge, no extraordinary circumstances exist.

ECONOMIC IMPACT:

An "Economic Impact" analysis of this action will be provided if requested by the Commissioner.

CERTIFICATION:

Vétoquinol certifies that this suitability petition contains all information known to them which is unfavorable to the petition.

03/01/2002

Pierre Gadbois d.m.v.
Manager, Regulatory Affairs

Vétoquinol N.-A. Inc.
2000 chemin Georges
Lavaltrie, Qc, Canada
J0K 1H0

Attachments

1. Pioneer Product Label
2. Proposed Product Label

ATTACHMENT I

Fort Dodge's Cefa-Drops® Labeling

Enlarged 115%
Page 1 of 2

NADA 140-684 and NADA 119-688, Approved by FDA

FORT DODGE®

Cefa-Drops®
CEFADROXIL
Veterinary Powder for Oral Suspension

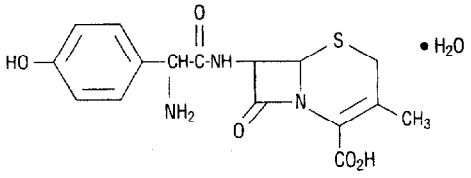
Cefa-Tabs®
CEFADROXIL
Veterinary Tablets

Cefa-Tabs®
CEFADROXIL
Veterinary Film-Coated Tablets

CEFA-DROPS (cefadroxil) and CEFA-TABS (cefadroxil) contain a semi-synthetic cephalosporin antibiotic intended for oral administration. CEFA-DROPS has an orange-pineapple flavor.

CHEMISTRY

Cefadroxil is a member of a group of semi-synthetic derivatives of cephalosporin C, found among the metabolic products of the fungus *Cephalosporium acremonium*. The cephalosporins are structurally related to the penicillins in that both contain a 4-member beta-lactam ring. Cefadroxil is a 7-amino cephalosporanic acid substituted at the 7 position to form a molecule designated chemically as (6R, 7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid monohydrate:



CLINICAL PHARMACOLOGY

Action

Cefadroxil, like other beta-lactam antibiotics, is a bactericidal agent that causes death of bacterial cells through a diversity of biological and biochemical effects on the cell wall. The spectrum of antibacterial activity includes many gram-negative organisms since cefadroxil, like other cephalosporins, has the ability to penetrate the outer envelope of gram-negative bacilli, thereby gaining access to cell wall target sites. Cefadroxil is generally not broken down by penicillinases such as those produced by penicillin-resistant staphylococci, although cephalosporinases have been identified that can inactivate the molecule.

Microbiology

The effectiveness of CEFA-DROPS and CEFA-TABS in skin and soft tissue infections caused by *Staphylococcus aureus*, (including penicillin-resistant strains) and in urinary tract infections caused by *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis*, has been demonstrated clinically in the dog. In cats, the effectiveness of cefadroxil in skin and soft tissue infections caused by susceptible pathogens such as *Pasteurella multocida*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus* spp. has also been demonstrated. In addition, cefadroxil has a broad spectrum of activity against both gram-positive and gram-negative human isolates. Although the clinical significance of *in vitro* data is unknown in the target species, the following human isolates are generally susceptible to cefadroxil at the indicated concentrations[1].

Organism	No. of Isolates	Minimum Inhibitory Concentration (mcg/mL) Range	MIC_{90}*
Streptococcus pyogenes	(24)	0.063-0.125	0.11
Streptococcus agalactiae	(27)	0.25-1	0.92
Streptococcus pneumoniae	(29)	0.5-2	1.2
Staphylococcus aureus, penicillin sensitive	(16)	2-16	3.2
Staphylococcus aureus, penicillin resistant	(63)	1-32	6.2
Staphylococcus epidermidis	(28)	0.125-4	2.13
Escherichia coli	(59)	4->125	16.0
Proteus mirabilis	(62)	4->125	15.6
Klebsiella pneumoniae	(61)	4-16	7.85
Salmonella spp.	(22)	4-8	7.19
Shigella spp.	(12)	2-8	6.98
Pasteurella multocida	(2)		1.4

*Concentration at which 90% of the isolates are susceptible.

The susceptibility of organisms to cefadroxil should be determined using the cephalosporin class disc, 30 mcg. Specimens for susceptibility testing should be collected prior to the initiation of antibiotic therapy.

Pharmacokinetics

Cefadroxil is stable in gastric acid and only moderately bound to serum proteins (approximately 20%). Cefadroxil is well absorbed from the gastrointestinal tract even when administered with food. The drug is excreted largely unchanged by the kidney. In humans, high concentrations of cefadroxil activity are found in urine within three hours after oral dosage[2]. The concurrent administration of probenecid retards the elimination rate.

In dogs, oral administration of cefadroxil at a dosage of 10 mg/lb results in mean peak serum concentrations averaging 18.6 mcg/mL within 1 to 2 hours after treatment[3]. The serum half-life ($T^1/_2$) following oral administration is approximately 2 hours. Over 50% of an orally administered dose is excreted unchanged in the urine of dogs within 24 hours. Serum concentration time profiles in dogs following oral administration are illustrated graphically in Figure 1.

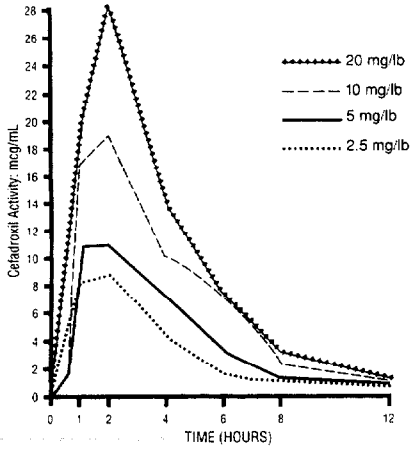


Figure 1: Cefadroxil Serum Concentration Curves in Dogs[3]

In cats, oral administration of cefadroxil at a dosage of 10 mg/lb results in peak serum concentrations of 17.4 mcg/mL within 1 to 2 hours after treatment. The serum half-life ($T^1/_2$) following oral administration to cats is $2^1/_2$ to 3 hours. Serum concentration time profiles in cats following oral administration are illustrated graphically in Figure 2.

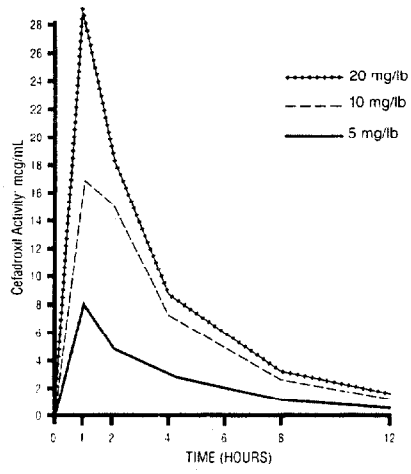


Figure 2: Cefadroxil Serum Concentration Curves in Cats

INDICATIONS

CEFA-DROPS (cefadroxil) and CEFA-TABS (cefadroxil) are indicated for the treatment of the following conditions:

Dogs: Genitourinary tract infections (cystitis) caused by susceptible strains of *Escherichia coli, Proteus mirabilis* and *Staphylococcus aureus.*

Skin and soft tissue infections including cellulitis, pyoderma, dermatitis, wound infections and abscesses caused by susceptible strains of *Staphylococcus aureus.*

Cats: Skin and soft tissue infections including abscesses, wound infections, cellulitis and dermatitis caused by susceptible strains of *Pasteurella multocida, Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus* spp.

CONTRAINDICATIONS

CEFA-DROPS and CEFA-TABS should not be administered to dogs or cats with a known allergy to cephalosporins. In penicillin-allergic animals, CEFA-DROPS and CEFA-TABS should be used with caution.

WARNINGS

For use in dogs and cats only. Not to be used in animals which are raised for food production. Safety for use in pregnant female dogs and cats or in breeding males has not been determined (see ANIMAL TOXICOLOGY).

ANIMAL TOXICOLOGY

In subacute studies, dogs administered 100, 200 or 400 mg/kg/day for 13 weeks showed no consistent or distinct treatment-related histopathologic changes. In chronic toxicity studies, dogs receiving doses as high as 600 mg/kg/day for six months showed no discernible treatment-related effects, with the exception of emesis in dogs receiving a 400 mg/kg/day dose at one time. No distinct or consistent meaningful drug-related changes in the hematologic, coagulation or urinalysis test results or in histologic examination of tissues were observed when compared to controls.

No teratogenic or antifertility effects were seen in reproductive studies done in mice and rats receiving dosages as high as nine times the maximum recommended canine dosage.

In cats, oral administration of cefadroxil at a dosage of 240 mg/kg/day divided into two equal doses (ten times the recommended daily dosage) for 21 consecutive days produced no clinical chemistry, pathological or other signs of toxicity other than reduced food consumption, vomiting and diarrhea.

ADVERSE REACTIONS

Occasional nausea and vomiting have been reported following cefadroxil therapy. Administration with food appears to decrease nausea. Diarrhea and lethargy have been occasionally reported.

DOSAGE

Dogs: CEFA-DROPS and CEFA-TABS 1 gram, 50 mg, 100 mg and 200 mg should be administered orally at a dosage of 10 mg/lb of body weight twice daily. Dogs with skin or soft tissue infections should be treated for a minimum of three days. Genitourinary tract infections should be treated for a minimum of seven days with cefadroxil. Maximum duration of therapy should not exceed 30 days.

Cats: CEFA-DROPS and CEFA-TABS 50 mg and 100 mg should be administered orally at a dosage of 10 mg/lb of body weight once daily. Maximum duration of therapy should not exceed 21 days.

In both species, drug treatment should continue for at least 48 hours after the animal is afebrile or asymptomatic. If no response is observed after three days of treatment, therapy should be discontinued and the case should be re-evaluated.

TO PREPARE SUSPENSION

Tap bottle lightly to loosen powder. For 15 mL bottle, add 10.4 mL of water in two portions. For 50 mL bottle, add 34 mL of water in two portions. Shake well after each addition. After mixing, store in refrigerator. Shake well before use. Discard unused portion after 14 days.

Droppers supplied with CEFA-DROPS are calibrated in mL increments. When mixed as directed, each mL contains cefadroxil monohydrate equivalent to 50 mg cefadroxil.

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian. The enclosed dose dropper in Cefa Drops contains natural rubber latex which may cause allergic reactions.

SUPPLY

CEFA-DROPS (cefadroxil) VETERINARY POWDER FOR ORAL SUSPENSION equivalent to:
NDC 0856-2365-20 – 750 mg cefadroxil per 15 mL dropper bottle
NDC 0856-2365-50 – 2500 mg cefadroxil per 50 mL dropper bottle

CEFA-TABS (cefadroxil) VETERINARY TABLETS
NDC 0856-2386-30 – 1 gram scored tablets, bottles of 20

CEFA-TABS (cefadroxil) VETERINARY FILM-COATED TABLETS
NDC 0856-2350-80 – 50 mg tablets, bottles of 500
NDC 0856-2351-80 – 100 mg tablets, bottles of 500
NDC 0856-2352-70 – 200 mg tablets, bottles of 250

Store at controlled room temperature 15° to 30°C (59° to 86°F).

REFERENCES

1. Leitner, F., et al: "Comparative antibacterial spectrum of cefadroxil." *J. Antimicrob. Chemother.* 10, Suppl. B, 1 (1982).
2. Harstein, A.L., et al: "Comparison of pharmacological and antimicrobial properties of cefadroxil and cephalexin." *Antimicrob. Agents Chemother.* 12, 93 (1977).
3. Gingerich, D. A.: "Clinical pharmacology of the cephalosporins and their present use in veterinary medicine." *College of Veterinary Medicine Review,* Mississippi State University, 2, 93 (1982).

U.S. Patent No. 4,504,657
Manufactured for
Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA
by Bristol-Myers Barceloneta, Inc.
Barceloneta, PR 00708

00330 Rev. October 1999 4230D

ATTACHMENT II

Generic Product Cefadroxil Paste Labeling

VETOQUINOL CEFADROXIL PASTE *DRAFT LABEL*

Veterinary Paste for Oral Administration

CEFADROXIL PASTE (cefadroxil) contains a semi-synthetic cephalosporin antibiotic intended for oral administration.

CHEMISTRY

Cefadroxil is a member of a group of semi-synthetic derivatives of cephalosporin C, found among the metabolic products of the fungus *Cephalosporium acremonium.* The cephalosporins are structurally related to the penicillins in that both contain a 4-member beta-lactam ring. Cefadroxil is a 7-amino cephalosporanic acid substituted at the 7 position to form a molecule designated chemically as (6R,7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid monohydrate:

[CHEMICAL STRUCTURE TO BE INSERTED HERE]

CLINICAL PHARMACOLOGY

Action

Cefadroxil, like other beta-lactam antibiotics, is a bactericidal agent that causes death of bacterial cells through a diversity of biological and biochemical effects on the cell wall. The spectrum of antibacterial activity includes many gram-negative organisms since cefadroxil, like other cephalosporins, has the ability to penetrate the outer envelope of gram-negative bacilli, thereby gaining access to cell wall target sites. Cefadroxil is generally not broken down by penicillinases such as those produced by penicillin-resistant staphylococci, although cephalosporinases have been identified that can inactivate the molecule.

Microbiology

The effectiveness of cefadroxil in skin and soft tissue infections caused by *Staphylococcus aureus,* (including penicillin-resistant strains) and in urinary tract infections caused by *Staphylococcus aureus, Escherichia coli* and *Proteus mirabilis,* has been demonstrated clinically in the dog. In cats, the effectiveness of cefadroxil in skin and soft tissue infections caused by susceptible pathogens such as *Pasteurella multocida, Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus* spp. has also been demonstrated. In addition, cefadroxil has a broad spectrum of activity against both gram-positive and gram-negative human isolates. Although the clinical significance of *in vitro* data is unknown in the target species, the following human isolates are generally susceptible to cefadroxil at the indicated concentrations'.

Organism	No. of Isolates	Minimum inhibitory Concentration (mcg/mL) Range	MIC_{90}*
Streptococcus pyogenes	(24)	0.063-0.125	0.11
Streptococcus agalactiae	(27)	0 25-1	0.92
Streptococcus pneumoniae	(29)	0.5-2	1.2
Staphylococcus aureus. Penicillin sensitive	(16)	2-16	3.2
Staphylococcus aureus penicillin resistant	(63)	1-32	6.2
Staphylococcus epidermidis	(28)	0.125-4	2.13
Escherichia coli	(59)	4->125	16.0
Proteus mirabilis	(62)	4->125	15.6
Klebsiella pneumoniae	(61)	4-16	7.85
Salmonella spp.	(22)	4-8	7.19
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Pasteurella multocida	(2)		1.4

*Concentration at which 90% of the isolates are susceptible.

The susceptibility of organisms to cefadroxil should be determined using the cephalosporin class disc, 30 mcg. Specimens for susceptibility testing should be collected prior to the initiation of antibiotic therapy.

Pharmacokinetics

Cefadroxil is stable in gastric acid and only moderately bound to serum proteins (approximately 20%). Cefadroxil is well absorbed from the gastrointestinal tract even when administered with food. The drug is excreted largely unchanged by the kidney. In humans, high concentrations of cefadroxil activity are found in urine within three hours after oral dosage[2]. The concurrent administration of probenecid retards the elimination rate.

In dogs, oral administration of cefadroxil at a dosage of 10 mg/lb results in mean peak serum concentrations averaging 18.6 mcg/mL within 1 to 2 hours after treatment[3]. The serum half-life (T½) following oral administration is approximately 2 hours. Over 50% of an orally administered dose is excreted unchanged in the urine of dogs within 24 hours. Serum concentration time profiles in dogs following oral administration are illustrated graphically in Figure 1.

[INSERT FIGURE 1 HERE]

Figure 1: Cefadroxil Serum Concentration Curves in Dogs[3]

In cats, oral administration of cefadroxil at a dosage of 10 mg/lb results in peak serum concentrations of 17.4 mcg/mL within 1 to 2 hours after treatment. The serum half-life (T½) following oral administration to cats is 2½ to 3 hours. Serum concentration time profiles in cats following oral administration are illustrated graphically in Figure 2.

[INSERT FIGURE 2 HERE]

Figure 2: Cefadroxil Serum Concentration Curves in Cats

INDICATIONS

Cefadroxil Paste is indicated for the treatment of the following conditions:

Dogs: Genitourinary tract infections (cystitis) caused by susceptible strains of *Escherichia coli, Proteus mirabilis* and *Staphylococcus aureus*.

Skin and soft tissue infections including cellulitis. pyoderma, dermatitis, wound infections and abscesses caused by susceptible strains of *Staphylococcus aureus*.

Cats: Skin and soft tissue infections including abscesses, wound infections, cellulitis and dermatitis caused by susceptible strains of *Pasteurella multocida, Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus* spp.

CONTRAINDICATIONS

Cefadroxil should not be administered to dogs or cats with a known allergy to cephalosporins. In penicillin-allergic animals, cefadroxil should be used with caution.

WARNINGS

For use in dogs and cats only. Not to be used in animals which are raised for food production. Safety for use in pregnant female dogs and cats or in breeding males has not been determined (see ANIMAL TOXICOLOGY).

ANIMAL TOXICOLOGY

In subacute studies, dogs administered 100, 200 or 400 mg/kg/day for 13 weeks showed no consistent or distinct treatment-related histopathologic changes. In chronic toxicity studies, dogs receiving doses as high as 600 mg/kg/day for six months showed no discernible treatment-related effects, with the exception of emesis in dogs receiving a 400 mg/kg/day dose at one time. No distinct or consistent meaningful drug-related changes in the hematologic, coagulation or urinalysis test results or in histologic examination of tissues were observed when compared to controls.

No teratogenic or antifertility effects were seen in reproductive studies done in mice and rats receiving dosages as high as nine times the maximum recommended canine dosage.

In cats, oral administration of cefadroxil at a dosage of 240 mg/kg/day divided into two equal doses (ten times the recommended daily dosage) for 21 consecutive days produced no clinical chemistry, pathological or other signs of toxicity other than reduced food consumption, vomiting and diarrhea.

ADVERSE REACTIONS

Occasional nausea and vomiting have been reported following cefadroxil therapy. Administration with food appears to decrease nausea. Diarrhea and lethargy have been occasionally reported.

DOSAGE

Dogs: Cefadroxil paste should be administered orally at a dosage of 10 mg/lb of body weight twice daily. Dogs with skin or soft tissue infections should be treated for a minimum of three days. Genitourinary tract infections should be treated for a minimum of seven days with cefadroxil. Maximum duration of therapy should not exceed 30 days.

Cats: Cefadroxil paste should be administered orally at a dosage of 10 mg/lb of body weight once daily. Maximum duration of therapy should not exceed 21 days.

In both species, drug treatment should continue for at least 48 hours after the animal is afebrile or asymptomatic. If no response is observed after three days of treatment, therapy should be discontinued and the case should be re-evaluated.

DOSAGE ADMINISTRATION

The syringe containing the Cefadroxil Paste uses an adjustable ring to deliver the desired amount of paste. Each mL contains cefadroxil monohydrate equivalent to 20 or 100 mg cefadroxil.

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

HOW SUPPLIED

Cefadroxil Paste is supplied in syringes with an adjustable ring to deliver the desired dose. Two concentrations of paste are provided with each mL of paste containing cefadroxil monohydrate equivalent to 20 or 100 mg cefadroxil.

Store at controlled room temperature 15° to 30°C (59° to 86°F). (TO BE VERIFIED)

REFERENCES

1. Leitner, F., et al: "Comparative antibacterial spectrum of cetadroxil." J. *Antimicrob. Chemother. 10,* Suppl. B,1 (1982).
2. Harstein, A.L., et al: "Comparison of pharmacological and antimicrobial properties of cefadroxil and cephalexin." *Antimicrob. Agents Chemother.* 12, 93 (1977).
3. Gingerich, D. A.: "Clinical pharmacology of the cephalosporins and their present use in veterinary medicine." *College of Veterinary Medicine Review,* Mississippi State University. 2, 93 (1982).