CONVENIA®
(cefovecin sodium)

Antimicrobial for Subcutaneous Injection in Dogs and Cats Only

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

DESCRIPTION: Cefovecin sodium is a semi-synthetic broad-spectrum antimicrobial agent from the cephalosporin class of chemotherapeutic agents. Cefovecin is the non-proprietary designation for (6R,7R,8S,9R,10S)-[2-[[(3R,4S,5R)-5-(6-methoxy-1,3-benzodioxole-2-y)carbonyl]amino]-3-[(2S,3S,4S,5R)-3-(2-thio-1-azoniazacyclo-4,2,1-triazol-2-ene-2-carboxylic acid, monosodium salt.

Figure 1: Chemical structure of cefovecin sodium.

Each mL of CONVENIA reconstituted lyophile contains cefovecin sodium equivalent to 80 mg cefovecin, methylenparaben 1.8 mg (preservative), propylparaben 0.2 mg (preservative), sodium citrate dihydrate 5.8 mg and citric acid monohydrate 0.1 mg, sodium hydroxide or hydrochloric acid as required to adjust pH.

INDICATIONS:

Dogs
CONVENIA is indicated for the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of Staphylococcus intermedius and Strepococcus canis (Group G).

Cats
CONVENIA is indicated for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of Pasteurella multocida.

DOSEAGE AND ADMINISTRATION:

Dogs
CONVENIA should be administered as a single subcutaneous injection of 3.6 mg/kg (8 mg/kg) body weight. A second subcutaneous injection of 3.6 mg/kg (8 mg/kg) may be administered if response to therapy is not complete. The decision for a second injection for any individual dog should take into consideration such factors as progress toward clinical resolution, the susceptibility of the causative organisms, and the integrity of the dog’s host-defense mechanisms.

Therapeutic drug concentrations after the first injection are maintained for 7 days for S. intermedius infections and for 14 days for S. canis (Group G) infections. Maximum treatment should not exceed 2 injections.

Cats
CONVENIA should be administered as a single, one-time subcutaneous injection at a dose of 3.6 mg/kg (8 mg/kg) body weight. After an injection of CONVENIA, therapeutic concentrations are maintained for approximately 7 days for Pasteurella multocida infections.

General Dosing Information
A sample of the lesion should be obtained for culture and susceptibility testing prior to beginning antimicrobial therapy.

Preparation of Solution for Injection: To deliver the appropriate dose, aseptically reconstitute CONVENIA with 10 mL Sterile Water for Injection. Shake and allow the vial to sit until all material is visually dissolved. The resulting solution contains cefovecin sodium equivalent to 80 mg/mL. CONVENIA is light sensitive. The vial should be stored in the original carton and refrigerated when not in use. Use the entire contents of the vial within 96 days of reconstitution.

Contraindications: CONVENIA is contraindicated in dogs and cats with known allergy to cephalosporins or to β-lactam (penicillins and cephalosporins) group antimicrobials. Anaphylaxis has been reported with the use of this product in foreign markets. If an allergic reaction or anaphylaxis occurs, CONVENIA should not be administered again and appropriate therapy should be instituted. Anaphylaxis may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine, corticosteroids, and airway management, as clinically indicated. Adverse reactions may require prolongation treatment due to the prolonged systemic drug clearance (85 days).

Warnings: Not for use in humans. Keep this and all drugs out of reach of children.

PRECAUTIONS:

Prescribing antimicrobial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant animal pathogens.

The safe use of CONVENIA in dogs or cats less than 6 months of age (see Animal Safety) and in breeding or lactating animals has not been determined. Safety has not been established for IM or IV administration. The long-term effects on injection sites have not been determined. CONVENIA is slowly eliminated from the body, approximately 85 days is needed to eliminate 97% of the administered dose from the body. Animals experiencing an adverse reaction may need to be monitored for this duration.

CONVENIA has been shown in an experimental in vitro system to result in an increase in free concentrations of caprophen, furosimide, dopamine, and ketaconazole. Concurrent use of these or other drugs that have a high degree of protein-binding (eg, NSAIDs, propylparaben, and cat behavior drugs) may require modification and cause adverse reactions. Positive direct Coombs’ test results and false positive reactions for glucose in the urine have been reported during treatment with some cephalosporin antimicrobials. Cephalosporin antimicrobials may also cause falsely elevated urine protein determinations. Some antimicrobials, including cephalosporins, can cause lowered albumin values due to interference with certain testing methods.

Occasionally, cephalosporins and NSAIDs have been associated with myelotoxicity, thereby creating a toxic neutropenia. Other hematological reactions seen with cephalosporins include neutropenia, anemia, hyperprothrombinemia, thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), platelet dysfunction and transient increases in serum aminotransferases.

Adverse Reactions:

Dogs
A total of 320 dogs, ranging in age from 6 weeks to 19 years, were included in a field study safety analysis. Adverse reactions reported in dogs treated with CONVENIA and the active control are summarized in Table 2.

Table 2: Number of Dogs* with Adverse Reactions Reported During the Field Study with CONVENIA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CONVENIA (n=147)</th>
<th>Active Control (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethargy</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia/Decreased Appetite</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased Burburism</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Cats
A total of 281 cats, ranging in age from 2.4 months (one cat) to 21 years, were included in the field study safety analysis. Adverse reactions reported in cats treated with CONVENIA and the active control are summarized in Table 3.

Table 3: Number of Cats* with Adverse Reactions Reported During the Field Study with CONVENIA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CONVENIA (n=144)</th>
<th>Active Control (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Anorexia/Decreased Appetite</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Lethargy</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hypo/Anoacting Strang</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inappropriate Umrination</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Some cats may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in dogs and cats in foreign markets: death, tremors/ataxia, seizures, anaphylaxis, acute pulmonary edema, facial edema, injection site reactions (alopecia, scabs, necrosis, and erythema), hemolytic anemia, salivation, pruritus, lethargy, vomiting, diarrhea, and inappetence.

Contact Information: For a copy of the Safety Data Sheet or to report adverse reactions, call Zoetis Inc. at 1-888-963-9471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or at www.fda.gov/reportadvs.

Clinical Pharmacology: Pharmacokinetics
Cefovecin is rapidly and completely absorbed following subcutaneous administration. Non-linear kinetics is exhibited (plasma concentrations do not increase proportionally with dose). Cefovecin does not undergo hepatic metabolism and the major route of elimination is the kidney. Cefovecin is a highly protein bound molecule in dog plasma (98.5%) and cat plasma (99.8%) and may compete with other highly protein bound drugs for plasma protein binding sites that could result in transient, higher free drug concentrations. Pharmacokinetic parameters following subcutaneous dosing at 8 mg/kg in the dog and cat are summarized in Table 4.

Table 4: Pharmacokinetic Parameters Reflecting Total Drug Concentrations in Plasma (mean ± standard deviation or range) Following an 8 mg/kg Intravenous or Subcutaneous Dose of Cefovecin in Dogs and Cats

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>MEAN ± SD or (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal plasma elimination half-life, T1/2 (h)</td>
<td>133 ± 16 or 106 ± 18</td>
</tr>
<tr>
<td>AUC (μg·h/mL)</td>
<td>10400 ± 1900 or 22700 ± 3450</td>
</tr>
<tr>
<td>Maximum concentration, Cmax (μg/mL)</td>
<td>6.2 ± (0.5-6.0) or 121 ± 51</td>
</tr>
<tr>
<td>Maximum concentration, Cmax (μg/mL)</td>
<td>141 ± 12 or 0.12 ± 0.01</td>
</tr>
<tr>
<td>(mean±SD) (range)</td>
<td>0.76 ± 0.13 or 0.350 ± 0.40</td>
</tr>
</tbody>
</table>

1 SD = standard deviation
2 a phase effect was observed, only data for the first phase are provided (n=6); all other data provided are derived from 12 animals
* = SC
** = IV
α = arithmetic mean
β = harmonic mean
γ = geometric mean
Population Pharmacokinetics

Dogs

Cefovecin plasma concentrations in the dog have been characterized by the use of population pharmacokinetic (PPK) data. Plasma cefovecin concentration data were pooled from four laboratory pharmacokinetic studies. The final dataset contained 338 concentration records from 22 dogs. The simulations from the model provide the mean population estimate and the 5th and 95th percentile of the population estimates of total and free cefovecin concentrations over time. Figure 2 shows the predicted free plasma concentrations following administration of 8 mg/kg body weight to dogs. Based upon these predicted concentrations, 95% of the canine population will have active (free) drug concentrations > the MIC₉₀ for S. canis (0.08 µg/mL) for approximately 14 days and free concentrations > the MIC₉₀ for S. intermedius (0.25 µg/mL) for approximately 7 days following a single 8 mg/kg subcutaneous injection of cefovecin. (See MICROBIOLOGY)

Figure 2: Population Predicted Free Concentration of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Dogs (solid line is population prediction, dotted lines are the 5th and 95th percentiles for the population prediction).

**Cats**

Cefovecin plasma concentrations in the cat have been characterized by the use of PPK data. Plasma cefovecin concentration data were pooled from four laboratory pharmacokinetic studies. The final dataset contained 338 concentration records from 22 cats. The simulations from the model provide the mean population estimate as well as the 5th and 95th percentile of the population estimates of total and free cefovecin concentrations over time. Figure 3 displays the predicted free plasma concentrations following administration of 8 mg/kg body weight to cats. Based upon these predicted concentrations, 95% of the feline population will have active (free) drug concentrations > the MIC₉₀ of Pasteurella multocida (0.06 µg/mL) for approximately 7 days when administered a single 8 mg/kg subcutaneous injection of cefovecin. (See MICROBIOLOGY)

Figure 3: Population Predicted Free Concentration of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Cats (solid line is population prediction, dotted lines are the 5th and 95th percentiles for the population prediction).

**Microbiology:**

**CONVENIA** is a cephalosporin antibiotic. Like other β-lactam antimicrobials, **CONVENIA** exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (e.g., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall. For *E. coli*, in the vibrio activity of **CONVENIA** is comparable to other cephalosporins, but due to the high-affinity protein-binding, the in vivo free concentration of cefovecin does not reach the MIC₉₀ for *E. coli* (1.0 µg/mL). **CONVENIA** is not active against Pseudomonas spp. or enterococci.

**Dogs**

The minimum inhibitory concentration (MIC) values for cefovecin against label-claim pathogens isolated from skin infections in dogs enrolled in a 2001-2003 field effectiveness study are presented in Table 5. All MICs were determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) standards.

**Cats**

The MIC values for cefovecin against Pasteurella multocida isolated from skin infections (wounds and abscesses) in cats enrolled in a 2001-2003 field effectiveness study are presented in Table 6. All MICs were determined in accordance with the CLSI standards.