CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
65115

DRAFT FINAL PRINTED LABELING
Cefadroxil monohydrate, USP is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to yellowish-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-(l-amino-4-hydroxy-phenyl)acetyl aminoo-3-methyl-8-oxo-7-oxocephalosporanate, (6R,6aR,10aR)-. It has the formula \(^{2}C_{13}H_{17}NO_{8}^{+}\cdot H_{2}O\) and the molecular weight of 381.40. It has the following structural formula:

Each 5 ml of reconstituted suspension for oral administration contains cefadroxil monohydrate equivalent to 125 mg, 250 mg or 500 mg of cefadroxil. In addition, Cefadroxil for Suspension contains the following inactive ingredients: colloidal silicon dioxide, FD&C yellow No. 6, aluminum sheets, flavoring, flavor base, sodium benzoate, sucrose, xanthan gum.

**CLINICAL PHARMACOLOGY**

Cefadroxil monohydrate is rapidly absorbed after oral administration. Following single doses of 500 mg and 1000 mg, average peak serum concentrations were approximately 16 and 28 mcg/mL, respectively. Measurable levels were present 12 hours after administration. Over 90% of the drug is excreted unchanged in the urine within 24 hours. Peak urine concentrations are approximately 1800 mcg/mL during the period following a single 500-mg oral dose. Increases in dosage generally produce a proportionate increase in cefadroxil monohydrate urinary concentration. The urine antibiotic concentration, following a 1-g dose, was maintained well above the MIC of susceptible urinary pathogens for 20 to 22 hours.

**Microbiology**

In vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cefadroxil has been shown to be active against the following organisms both in vitro and in clinical infections (see INDICATIONS AND USAGE):

- Beta-lactamase-producing strains
- Streptococcus (Diplococcus) pneumoniae
- Escherichia coli
- Proteus mirabilis
- Klebsiella species
- Moraxella (Branhamella) catarrhalis

**Susceptibility tests: Dilution techniques**

The use of antibiotic disk susceptibility test methods which measure zone diameter give an accurate estimation of antibiotic susceptibility. One such standard procedure which has been recommended for use with disks to test susceptibility of organisms to cefadroxil monohydrate uses the cephalosporin class (cephalaxin) disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefadroxil monohydrate.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 mcg cephalothin disk should be interpreted according to the following criteria:

- Zone Diameter (mm)
  - ≥18: (S) Susceptible
  - 15-17: (I) Intermediate
  - ≤14: (R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable serum levels. A report of "Intermediate susceptibility" suggests that the organism would be susceptible if high dosages is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 mcg cephalothin disk should give the following zone diameters:

<table>
<thead>
<tr>
<th>Organism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus ATCC 25923</td>
<td>≥17</td>
</tr>
<tr>
<td>Escherichia coli ATCC 25922</td>
<td>≤17-22</td>
</tr>
</tbody>
</table>

**INDICATIONS AND USAGE**

Cefadroxil monohydrate is indicated for the treatment of patients with infection caused by susceptible strains of the designated organisms in the following diseases:

- Upper and lower respiratory tract infections caused by E. coli, P. mirabilis, and Klebsiella species
- Skin and skin structure infections caused by staphylococci and/or streptococci
- Pharyngitis and/or tonsillitis caused by Streptococcus pyogenes (Group A beta-hemolytic streptococcus)

**CONTRAINDICATIONS**

Cefadroxil monohydrate is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

**WARNINGS**

BEFORE THERAPY WITH CEFADROXIL MONOHYDRATE IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFADROXIL, CEPHALOSPORINS, PENCILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENCILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENCILLIN ALERGY.

IF AN ALLERGIC REACTION TO CEFADROXIL MONOHYDRATE OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS EPINEPHRINE, SYNTHETIC ADRENALENOIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefadroxil, and may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of Clostridium difficile. Studies indicated that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against Clostridium difficile.

**PRECAUTIONS**

Cefadroxil monohydrate should be used with caution in the presence of markedly impaired renal function (creatinine clearance < 30 mL/min, 1.73 M²). See (DOSE AND ADMINISTRATION.) In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prolonged use of cefadroxil monohydrate may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefadroxil monohydrate should be prescribed with caution in individuals with history of gastrointestinal disease, particularly colitis.

**Drug/Laboratory Test Interactions**

Directly active Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hemostatic studies or in transfusion cross-matching procedures when antibody tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility**

No long-term studies have been performed to determine carcinogenic potential. No genetic toxicity tests have been performed.

**Pregnancy**

Pregnancy Category B

Reproduction studies have been performed in mice and rats at doses up to 11 times
the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefadroxil monohydrate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery**

Cefadroxil monohydrate has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

**Nursing Mothers**

Caution should be exercised when cefadroxil monohydrate is administered to a nursing mother.

**Pediatric Use**

(See DOSAGE AND ADMINISTRATION.)

**Geriatric Use**

Of approximately 650 patients who received cefadroxil monohydrate for the treatment of urinary tract infections in three clinical trials, 28% were 60 years and older, while 16% were 70 years and older. Of approximately 1000 patients who received cefadroxil monohydrate for the treatment of skin and skin structure infections in 14 clinical trials, 12% were 60 years and older while 4% were 70 years and older. No overall differences in safety were observed between the elderly patients in these studies and younger patients. Clinical studies of cefadroxil monohydrate for the treatment of pharyngitis or tonsillitis did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger patients. Other reported clinical experience with cefadroxil monohydrate has not identified differences in response between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Cefadroxil monohydrate is substantially excreted by the kidney, and dosage adjustment is indicated for patients with renal impairment (see DOSAGE AND ADMINISTRATION). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

### ADVERSE REACTIONS

**Gastrointestinal**

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Dyspepsia, nausea and vomiting have been reported rarely. Cholestatic jaundice has also occurred.

**Hypersensitivity**

Allergies (in the form of rash, urticaria, angioedema, and pruritus) have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

**Other**

Other reactions have included hepatic dysfunction including cholestasis and elevations in serum transaminase, galactosaemia, galactosuria, hypoglycemia, moderate transient neutropenia, and allergic reactions (urticaria, angioedema, pseudolymphocytic hives, failure, erythema multiforme, Stevens-Johnson syndrome, sepsis, skin necrosis, pruritus, and arthralgia) have been rarely reported.

In addition to the adverse reactions listed above, which have been observed in patients treated with cefadroxil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

- **Toxic epidermal necrolysis, abdominal pain, superinfection, renal dysfunction, toxic epidermal necrolysis, aplastic anemia, hemolytic anemia, hemoglobinuria, prolonged prothrombin time, positive Coombs’ test, increased bilirubin, increased alkaline phosphatase, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated bilirubin, elevated LDH, eosinophilia, pancytopenia, neutropenia.**

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSE). If seizures are associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

**OVERDOSE**

A study of children under six years of age suggested that ingestion of less than 250 mg/kg of cephalosporin is not associated with significant outcomes. No action is required other than general support and observation. For amounts greater than 250 mg/kg, induce gastric emptying.

In five anuric patients, it was demonstrated that an average of 63% of a 1 g oral dose is extracted from the body during a 6-8 hour hemodialysis session.

**DOSAGE AND ADMINISTRATION**

Cefadroxil monohydrate is acid-stable and may be administered orally without regard to meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

**Adults**

**Urinary Tract Infections:** For uncomplicated lower urinary tract infections (i.e., cystitis) the usual dosage is 1 or 2 g per day in a single (q.d.) or divided doses (b.i.d.).

**Skin and Skin Structure Infections:** For skin and skin infections the usual dosage is 1 g per day in single (q.d.) or divided doses (b.i.d.).

**Pharyngitis and Tonsillitis:** Treatment of group A beta-hemolytic streptococcal pharyngitis and tonsillitis — 1 g per day in single (q.d.) or divided doses (b.i.d.).

**Children**

For urinary tract infections, the recommended daily dosage for children is 30 mg/kg/day in divided doses every 12 hours for pharyngitis, tonsillitis, and impetigo, the recommended daily dosage for children is 20 mg/kg/day in a single dose or in equally divided doses every 12 hours. For skin and skin structure infections, the recommended daily dosage is 30 mg/kg/day in equally divided doses every 12 hours. In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of cefadroxil monohydrate should be administered for at least 10 days.

See chart for total daily dosage for children.

<table>
<thead>
<tr>
<th>Child’s Weight</th>
<th>125 mg/5 mL</th>
<th>250 mg/5 mL</th>
<th>500 mg/5 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>lbs</td>
<td>kg</td>
<td>125 mg/5 mL</td>
<td>250 mg/5 mL</td>
</tr>
<tr>
<td>10</td>
<td>4.5</td>
<td>1 tsp</td>
<td>---</td>
</tr>
<tr>
<td>20</td>
<td>9.1</td>
<td>2 tsp</td>
<td>1 tsp</td>
</tr>
<tr>
<td>30</td>
<td>13.6</td>
<td>3 tsp</td>
<td>1 1/2 tsp</td>
</tr>
<tr>
<td>40</td>
<td>18.2</td>
<td>4 tsp</td>
<td>2 tsp</td>
</tr>
<tr>
<td>50</td>
<td>22.7</td>
<td>5 tsp</td>
<td>2 1/2 tsp</td>
</tr>
<tr>
<td>60</td>
<td>27.3</td>
<td>6 tsp</td>
<td>3 tsp</td>
</tr>
<tr>
<td>70 &amp; above</td>
<td>31.8</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

**Renal Impairment:**

In patients with renal impairment, the dosage of cefadroxil monohydrate should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg of cefadroxil monohydrate and the maintenance dose (based on the creatinine clearance rate (mL/min/1.73 M2)) is 500 mg at the time intervals listed below.

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dosage Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-10 mL/min</td>
<td>36 hours</td>
</tr>
<tr>
<td>10-25 mL/min</td>
<td>24 hours</td>
</tr>
<tr>
<td>25-50 mL/min</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

**HOW SUPPLIED**

Cefadroxil For Oral Suspension, USP is available in:

- The 125 mg per 5 mL of reconstituted suspension* contains cefadroxil monohydrate equivalent to 125 mg with a light orange colored powder forming orange suspension on constitution with water. The resulting suspension has a characteristic mixed fruit flavor and is available as follows:
  - NDC 63304-972-04
  - 100 mL bottles

- The 250 mg per 5 mL of reconstituted suspension* contains cefadroxil monohydrate equivalent to 250 mg with a light orange colored powder forming orange suspension on constitution with water. The resulting suspension has a characteristic mixed fruit flavor and is available as follows:
  - NDC 63304-973-04
  - 100 mL bottles

- The 500 mg per 5 mL of reconstituted suspension* contains cefadroxil monohydrate equivalent to 500 mg with a light orange colored powder forming orange suspension on constitution with water. The resulting suspension has a characteristic mixed fruit flavor and is available as follows:
  - NDC 63304-974-01
  - 75 mL bottles
  - NDC 63304-974-04
  - 100 mL bottles

* Shake ORAL SUSPENSION WELL BEFORE USING. Keep bottle tightly closed. After reconstitution, store in refrigerator. Any unused portion of the reconstituted suspension must be discarded after 14 days.

Prior to reconstitution, Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).

**References**


Manufactured for:

Rainbaxy Pharmaceuticals Inc.
Princeton, NJ 08540 USA
By: Rainbaxy Laboratories Limited
New Delhi - 110 019, India
August 2002
CEFAROXIL
100 mL (when mixed)
For Oral Suspension USP
Rx only

125 mg/5 mL

DO NOT USE IF FOIL SEAL IS BROKEN OR MISSING FROM BOTTLE.

Store sealed. Store dry powder at controlled room temperature 10° to 30°C (50° to 86°F) (See USP).

Shake well before use.

Store unopened bottle until all powder has been used.

Add approximately 70 mL of water for reconstitution (2 oz = 70 mL). Shake vigorously to wet powder. Add remaining water; stir until dissolved.

When reconstituted, each 5 mL, approximately 1 teaspoonful, will contain 625 mg of cefadroxil

Manufactured for:

Hospira Pharmaceuticals Inc.
Plainview, NY 11803 USA
50200-920

Shake well before usage. Any unused portion of the reconstituted suspension should be discarded after 14 days.

SHELF LIFE: 36 months

100-MG SOFT GELATIN FOR ORAL SUSPENSION USP

125-mg/mL. Over size bottle provides extra space for shaking bottle tightly closed. After reconstitution, store in refrigerator. Shake well before usage. Any unused portion of the reconstituted suspension should be discarded after 14 days.

SHAKE WELL BEFORE USING

125 mg/5 mL