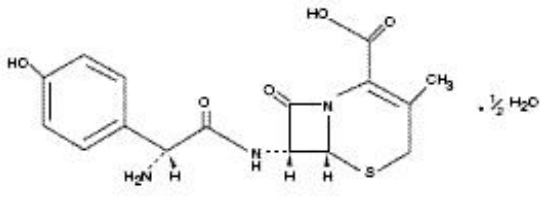
CEFADROXIL - cefadroxil hemihydrate capsule
Physicians Total Care, Inc.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefadroxil Tablets and Cefadroxil Capsules and other antibacterial drugs, Cefadroxil Tablets and Cefadroxil Capsules should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Cefadroxil**,** USP (hemihydrate) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is white to off-white crystalline powder. It is slightly 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-[[amino (4-hydroxyphenyl) acetyl] amino]-3- methyl-8-oxo-, hemihydrate, [6R-[6α, 7β (R*)]]-. It has the formula $C_{16}H_{17}N_3O_5S$•½ H_2O and the molecular weight of 372.39. It has the following structural formula:



Each film coated tablet for oral administration contains Cefadroxil hemihydrate equivalent to 1 gram cefadroxil. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, monosodium citrate, polyethylene glycol, talc and titanium dioxide.

Each capsule for oral administration contains Cefadroxil hemihydrate equivalent to 500 mg cefadroxil. In addition, each capsule contains the following inactive ingredients: magnesium stearate and pregelatinized starch.

The capsule shell also contains D&C yellow no. 10, FD&C blue no. 1, FD&C red no. 40, gelatin and titanium dioxide.

The imprinting ink also contains D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, pharmaceutical glaze, propylene glycol and synthetic black iron oxide.

CLINICAL PHARMACOLOGY

Cefadroxil is rapidly absorbed after oral administration. Following single doses of 500 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 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-hemolytic streptococci

Staphylococci, including penicillinase-producing strains

Streptococcus (Diplococcus) pneumoniae

Escherichia coli

Proteus mirabilis

Klebsiella species

Moraxella (Branhamella) catarrhalis

Note: Most strains of *Enterococcus faecalis* (formerly *Streptococcus faecalis*) and *Enterococcus faecium* (formerly *Streptococcus faecium*) are resistant to cefadroxil. It is not active against most strains of *Enterobacter* species, *Morganella morganii* (formerly *Proteus morganii*), and *P. vulgaris*. It has no activity against *Pseudomonas* species and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herella* species).
Susceptibility tests: Diffusion techniques

The use of antibiotic disk susceptibility test methods which measure zone diameter give an accurate estimation of antibiotic susceptibility. One such standard procedure[1] which has been recommended for use with disks to test susceptibility of organisms to cefadroxil uses the cephalosporin class (cephalothin) disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefadroxil.

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)	**Interpretation**
≥ 18	(S) Susceptible
15 to 17	(I) Intermediate
≤ 14	(R) Resistant

A report of “Susceptible” indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of “intermediate susceptibility” suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue 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:

Organism	**Zone Diameter (mm)**
Staphylococcus aureus ATCC 25923	29 to 37
*Escherichia coli ATCC 2*5922	17 to 22

Dilution Techniques

When using the NCCLS agar dilution or broth dilution (including microdilution) method[2] or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimum inhibitory concentration) value for cephalothin is 8 mcg/mL or less. Organisms are considered resistant if the MIC is 32 mcg/mL or greater. Organisms with an MIC value of less than 32 mcg/mL but greater than 8 mcg/mL are intermediate.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cephalothin powder should give MIC values in the range of 0.12 mcg/mL and 0.5 mcg/mL for *Staphylococcus aureus* ATCC 29213. For *Escherichia coli* ATCC 25922, the MIC range should be between 4 mcg/mL and 16 mcg/mL. For *Streptococcus faecalis* ATCC 29212, the MIC range should be between 8 and 32 mcg/mL.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefadroxil Tablets and Cefadroxil Capsules and other antibacterial drugs, Cefadroxil Tablets and Cefadroxil capsules should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

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

Urinary 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 Streptococci).

Note: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefadroxil is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefadroxil for the prophylaxis of subsequent rheumatic fever are not available.

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

Renal function studies should be performed when indicated.

CONTRAINDICATIONS

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

WARNINGS

BEFORE THERAPY WITH CEFADROXIL IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFADROXIL, CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-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 PENICILLIN ALLERGY.

IF AN ALLERGIC REACTION TO CEFADROXIL OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, 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 clostridia. Studies indicate 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

General:

Prescribing Cefadroxil Tablets and Cefadroxil Capsules in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Cefadroxil should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 mL/min/1.73 M^2) (See **DOSAGE 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 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 should be prescribed with caution in individuals with history of gastrointestinal disease, particularly colitis.

Drug /Laboratory Test Interactions

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin 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. 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 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 is administered to a nursing mother.

Geriatric Use

Of approximately 650 patients who received cefadroxil 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 for the treatment of skin and skin structure infection in 14 clinical trials, 12% were 60 years and older while 4% were 70 years and over. No

overall differences in safety were observed between the elderly patients in these studies and younger patients. Clinical studies of cefadroxil for the treatment for 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 has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Cefadroxil is substantially excreted by the kidney, and dosage adjustment is indicated for patients with renal impairment (see **DOSAGE AND ADMINISTRATION: Renal Impairment**). 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.

Pediatric Use

(See **DOSAGE AND ADMINISTRATION**).

Information for Patients

Patients should be counseled that antibacterial drugs including Cefadroxil Tablets and Cefadroxil Capsules should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Cefadroxil Tablets and Cefadroxil Capsules are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Cefadroxil Tablets and Cefadroxil Capsules or other antibacterial drugs in the future.

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. Diarrhea 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, genital pruritus, genital moniliasis, vaginitis, moderate transient neutropenia, fever. Agranulocytosis, thrombocytopenia,idiosyncratic hepatic failure, erythema multiforme, Stevens-Johnson syndrome, serum sickness, 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 nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, positive Coombs' test, increased BUN, increased creatinine, elevated 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 **OVERDOSAGE**). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

A study of children under six years of age suggested that ingestion of less than 250 mg/kg of cephalosporins 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 to 8 hour hemodialysis session.

DOSAGE AND ADMINISTRATION

Cefadroxil 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 single (q.d.) or divided doses (b.i.d).

For all other urinary tract infections the usual dosage is 2 g per day in divided doses (b.i.d).

Skin and Skin Structure Infections: For skin and skin structure 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) for 10 days.

Cefadroxil oral suspension may be more suitable for pediatric patients.
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 30 mg/kg/day in a single dose or in equally divided doses every 12 hours. For other 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 should be administered for at least 10 days.
Renal Impairment

In patients with renal impairment, the dosage of cefadroxil 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 and the maintenance dose (based on the creatinine clearance rate [mL/min/1.73 M^2]) is 500 mg at the time intervals listed below.

Creatinine Clearances	Dosage Interval
0 to 10 mL/min	36 hours
10 to 25 mL/min	24 hours
25 to 50 mL/min	12 hours

Patients with creatinine clearance rates over 50 mL/min may be treated as if they were patients having normal renal function.

HOW SUPPLIED

Cefadroxil capsules contain cefadroxil hemihydrate equivalent to 500 mg of cefadroxil and are supplied as follows:

Cefadroxil 500 mg Capsules: white opaque body and brown opaque cap imprinted with ‘C’ on the cap and ‘582’ on the body.

(10s) NDC 54868-3742-3

(15s) NDC 54868-3742-2

(20s) NDC 54868-3742-1

Dispense in a tight container as defined in the USP.

Store at 20 - 25° C (68 - 77° F). (See USP Controlled Room Temperature).

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard, *Performance Standards for Antimicrobial Disk Susceptibility Test*, 4th Edition, Vol. 10(7): M2-A4, Villanova, PA, April, 1990.

2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 10(8): M7-A2, Villanova, PA, April, 1990.

Manufactured for:

Ranbaxy Pharmaceuticals Inc.

Jacksonville, FL 32216 USA

by: Ranbaxy Laboratories Ltd.

New Delhi - 110 019, India

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Repackaging and Relabeling by:
Physicians Total Care, Inc.
Tulsa, OK 74146

PRINCIPAL DISPLAY PANEL

Cefadroxil 500 mg Capsules

CEFADROXIL

cefadroxil hemihydrate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-3742(NDC:63304-582)

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CEFADROXIL HEMIHYDRATE (UNII: J9CMF6461M) (CEFADROXIL - UNII:280111G160)	CEFADROXIL HEMIHYDRATE	500 mg

Inactive Ingredients

Ingredient Name	Strength
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	brown (brown opaque) , white (white opaque)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	C;582
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-3742-1	20 in 1 BOTTLE		
2	NDC:54868-3742-2	15 in 1 BOTTLE		
3	NDC:54868-3742-3	10 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065015	04/23/1996	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	repack, relabel