For the Use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

DROXYL

(Cefadroxil 500 mg Tablet)

COMPOSITION

DROXYL-500
Each uncoated tablet contains:
Cefadroxil I.P. equivalent to Cefadroxil Anhydrous..... 500 mg

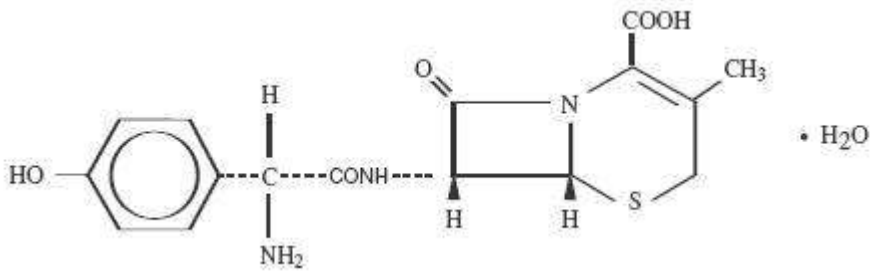
DESCRIPTION

Cefadroxil is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to off-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as (6 *R*,7*R*)-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

Molecular Formula: $C_{16}H_{17}N_3O_5S \bullet H_2O$

Molecular weight: 381.40

Structural Formula:



CLINICAL PHARMACOLOGY

PHARMACODYNAMIC

General properties

Pharmacotherapeutic group: Beta-lactam antibiotics, cephalosporins.

Cefadroxil is a cephalosporin for oral administration which inhibits bacterial wall synthesis of actively dividing cells by binding to one or more penicillin-binding proteins. The result is formation of a defective cell wall that is osmotically unstable, and bacterial cell lysis.

Breakpoints

The following MIC (Minimal Inhibitory Concentration) breakpoints according to NCCLS (National Committee for Clinical Laboratory Standards) separate susceptible (S) from intermediately susceptible and intermediately susceptible from resistant (R) organisms:

S $\leq$ 8mg/l and R $\geq$ 32 mg/l

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. The information in the table gives only approximate guidance as to whether microorganisms will be susceptible to cefadroxil.

Micro-organism	**Range of acquired resistance**
Susceptible	
Gram-positive aerobes	
Staphylococcus aureus (methicillin-susceptible)	0 - 11 %
Streptococci Group B, C and G	
Streptococcus pneumoniae	5,4 - 12,6 % (a)
Streptococcus pyogenes	
Gram-negative aerobes	
Moraxella catarrhalis	(2 %)
Intermediately susceptible	
Gram-negative aerobes	

Citrobacter diversus	
E. coli	0 - 80 %
H. influenzae	50 - 57 %
K. pneumoniae	2 - 50 %
K. oxytoca	7 - 22 %
P. mirabilis	0 - 90 %
Salmonella	
Shigella	
Resistant	
Gram-positive aerobes	
Enterococci	
Staphylococcus aureus (Methicillin-resistant)	
Staphylococcus epidermidis (Methicillin-resistant)	
Streptococcus pneumoniae (penicillin-resistant)	
Gram-negative aerobes	
Acinetobacter spp.	
Citrobacter freundii	
Enterobacter spp.	
Morganella morganii	
P. vulgaris	
Providencia rettgeri	
Providencia stuartii	
Pseudomonas aeruginosa	
Serratia marcescens	

(a) prevalence of penicillin-resistance in Concerned Member States

Resistance

Cefadroxil may be active against organisms producing some types of beta-lactamase, for example TEM-1, in low to moderate quantities. However, it is inactivated by beta-

lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes.

Cefadroxil cannot be expected to be active against bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam drugs. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

In vitro, oral first generation cephalosporins are less active than penicillins G and V on Gram-positive microorganisms and are less active than aminopenicillins on H. influenzae.

PHARMACOKINETICS

Cefadroxil is rapidly absorbed after oral administration. The bioavailability is unaffected by food. Measurable levels were present 12 hours after administration. Over 90% of the drug is excreted unchanged in the urine within 24 hours.

Increases in dose generally produce a proportionate increase in Cefadroxil urinary concentration. Oral dosing produces effective tissue penetration in lungs, tonsils, liver, gall bladder, bile duct, prostate, bone, muscle and synovial capsule as well as saliva, sputum, pleural exudate, bile and synovial fluid. The half-life is approximately 80-120 minutes and protein binding is approximately 20%.

INDICATIONS

Cefadroxil is indicated in the treatment of the following infections when due to susceptible micro-organisms:

<u>Respiratory tract infections:</u>

Tonsillitis, pharyngitis, lobar and bronchopneumonia, acute and chronic bronchitis, pulmonary abscess, empyema, pleurisy, sinusitis, laryngitis, otitis media.

<u>Skin and soft-tissue infections:</u>

Lymphadenitis, abscesses, cellulitis, decubitus ulcers, mastitis, furunculosis, erysipelas.

Genitourinary tract infections:

Pyelonephritis, cystitis, urethritis, gynaecological infections.

Other infections:

Osteomyelitis, septic arthritis.

CONTRAINDICATIONS

Cefadroxil is contra-indicated in patients with a history of hypersensitivity to any of the ingredients.

WARNING ABD PRECAUTION

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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefadroxil, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated

General

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 m2). In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prescribing cefadroxil tablets 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.

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.

Information for Patients

Patients should be counseled that antibacterial drugs including cefadroxil tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefadroxil tablets 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 or other antibacterial drugs in the future

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Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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.

DRUG INTERACTIONS

Cefadroxil should not be combined with bacteriostatic antibiotics (e.g. tetracycline, erythromycin, sulfonamides, chloramphenicol) since an antagonistic effect is possible.

Treatment with Cefadroxil in combination with aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics should be avoided since such combinations can potentiate nephrotoxic effects

Frequent checks on coagulation parameters are necessary during concomitant long term use of anticoagulants or thrombocyte aggregation inhibitors to avoid haemorrhagic complications.

The concomitant administration of probenicid can produce higher and sustained concentrations of cefadroxil in the serum and in the bile.

The occurence of diarrhoea may impair the resorption of other medicaments and therefore lead to an impairment of their efficacy.

Forced diuresis leads to a decrease of cefadroxil blood levels.

Cefadroxil may attenuate the effect of oral contraceptives.

Cefadroxil binds to cholestyramine which may lead to reduced bioavailability of cefadroxil.

Urine from patients treated with cefadroxil may give a false-positive glycosuria reaction when tested with Benedict's or Fehling's solutions. This does not occur with enzyme based tests.

ADVESRSE EVENT

Adverse drug reactions occur in about 6% to 7%* of treated patients.

Hypersensitivity reactions:

Common (>1/100, <1/10)
Pruritus, rash, allergic exanthema, urticaria.

Rare (>1/10 000, <1/1000)
Angioneurotic oedema, drug fever, serum sickness-like reactions, arthralgia, intertitial nephritis.

Very rare (<1/10 000)
Immediate allergic reaction (anaphylactic shock).
Isolated cases of Stevens Johnson syndrome and erythema multiforma have been reported.

Blood disorders:

Rare (>1/10 000, <1/1000)
Eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis: rare cases during prolonged used, which subside upon discontinuation of therapy.

Very rare (<1/10 000)
Isolated cases of haemolytic anaemia of immunologic origin.

Gastrointestinal disorders:

Common (>1/100, <1/10)
Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, glossitis.

Very rare (<1/10 000)
Isolated cases of pseudomenbranous colitis have been reported.

Liver disorders:

Rare (>1/10 000, <1/1000)
Minor elevation of serum transaminases (ASAT, ALAT) and alkaline phosphatases. Cases of cholestase and idiosyncratic hepatic failure have been reported.

CNS disorders

Very rare (<1/10 000)
Headache, dizziness, nervousness, sleeplessness, fatigue.

Other undesirable effects:
Uncommon (>1/1000, <1/100)

Clinical pictures due to a growth of opportunistic organisms (fungi), such as vaginal mycoses, thrush

*incidence of suspected adverse reactions in an observational post-marketing study in 904 patients.

OVERDOSE

Ingestion of < 250 mg/kg in children under six years of age was not associated with significant outcomes. The patient should be observed and treated symptomatically. For amounts > 250 mg/kg gastric lavage or stimulation of vomiting is appropriate

DOSAGE AND METHOD OF ADMINISTRATION

As per the physician direction.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

PREGNANCY AND NURSING MOTHER

There is no evidence of teratogenicity, the safe use of cefadroxil during pregnancy has not been established. Cefadroxil is excreted in breast milk and should be used with caution in lactating mothers.

Expiry date
Do not use later than the date of expiry.

Storage
KEEP IN A COOL DRY PLACE, PROTECTED FROM LIGHT

Presentation
DROXYL-500 is available in Strip of 10 Tablets

MARKETED BY:

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